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CLINICAL AND EXPERIMENTAL OBSERVATIONS ON FOCAL INFECTION, WITH AN ANALYSIS OF 200 CASES OF RHEUMATOID ARTHRITIS *

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FOCAL infection is a splendid example of a plausible medical theory which is in danger of being converted by its too enthusiastic supporters into the status of an accepted fact. Certainly the theory of focal infection has travelled a long way since it was first presented to the medical profession of America by Frank Billings[1] in his classic contribution, "Chronic Focal Infections and Their Etiological Relations to Arthritis and Nephritis." This article was published in the Archives of Internal Medicine in 1912 and marks the first important contribution to the subject in this country. Today, 25 years after publication of Billings' article, focal infection has come to occupy a very important place in the activities of medical and surgical practice and of the various specialties.

Many of us who originally accepted the theory of focal infection with enthusiasm have watched with interest and some trepidation its rapid development in the various fields of medicine but are now wondering if the time has not arrived for a revaluation of the whole theory. Many thoughtful students today question seriously its validity, and some are quite willing to throw it completely overboard. This is particularly true in Europe where the idea of focal infection has never met with enthusiastic acceptance. But even in America, the home of focal infection, scientific men are becoming a little wearied of the universal acceptance of a theory as though it were an established fact. For example, one of our leading pathologists has satirically described a focus of infection as "anything that is readily accessible for surgery." Another colleague recently remarked that the present medi-

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cal epoch would probably go down in history as the "Era of Focal Infection."

Foci of infection have been assumed to play a rôle in many diseases such as arthritis, iritis, rheumatic fever, nephritis, heart disease and bronchiectasis. However, we wish to limit our discussion to the relation of focal infection to rheumatoid arthritis, the disease with which it has been so intimately associated since the birth of the theory. For example, Billings in the article above referred to, reviewed 10 cases of arthritis in each of which he defined one or more foci of infection. All were greatly benefited or absolutely cured by removal of these foci. However, after careful reading of the histories of Billings' 10 cases, it is questionable just how many of them we would classify today as typical rheumatoid arthritis.

Not only Billings but most of the earlier writers reporting studies on the relation of focal infection to arthritis have failed to differentiate clearly "infectious" or "rheumatoid" arthritis from osteo-arthritis or various other forms of joint disease. In this paper we have included under the term "rheumatoid" only those patients who presented the picture of a chronic progressive inflammatory disease of several joints characterized in the early stages by periarticular swelling and fusiform fingers, and in the later stages by ankylosis and deformity.

In 1927 Cecil and Archer[2] made a report on 200 cases of "Chronic Infectious Arthritis" with special reference to the incidence of focal infection. These patients had all been studied in the Cornell Clinic at some time during the preceding five or six years. Today, 10 years later, we would probably omit many of them as not fulfilling the criteria of rheumatoid arthritis; for example, only 29 per cent of the cases in this study showed fusiform fingers, a clinical manifestation which we now consider almost pathognomonic of the disease. Infected tonsils were observed in 61 per cent, while infected teeth either alone or associated with other foci were noted in 33 per cent! Miscellaneous foci including infected sinuses were noted in 15 per cent of the cases. The tonsils were removed in 28 per cent of these cases as a therapeutic measure, but only one-half were cured or improved by the operation. Of the 21 cases that had teeth extracted, seven were cured and six improved. In this study on clinic patients, focal infections appear to have been very common and the removal of foci, especially when carried out early in the disease, seemed to produce beneficial results in a good proportion of cases. At that time these figures seemed striking and to have some significance, but in view of what we now know of the nature of arthritis, it is possible that a good many cases would have shown improvement even if the foci had not been removed.

Today we are faced with a different situation. Foci of infection are being rapidly disposed of by an army of energetic surgeons. Well might we exclaim, "Where are the foci of yesterday!" Comparatively rare in private practice is the sight of a tonsil either normal or diseased. How beautifully the teeth and gums are cared for! How unusual is the discovery

of a neglected case of sinusitis! And yet we still have rheumatoid arthritis with us. Certainly, in spite of all we have learned about focal infection, rheumatoid arthritis is still a very prevalent disease. It is for this reason that we wish to present a study of another 200 cases of rheumatoid arthritis from the records of the private practice of Dr. Cecil with special reference to the incidence of focal infection. All of the cases in this series have been observed within the last six or seven years, and in our opinion, form an interesting contrast to the 200 cases of infectious arthritis from the Cornell Clinic reported by Cecil and Archer a decade ago.

It is axiomatic, of course, that all infections have an original focus or portal of entry through which the microörganisms gain access to the body. The site of the portal of entry may be due to a very fleeting infection such as an acute coryza or influenza or it may be a chronic focus, such as a chronic sinus or apical abscess.

A classic example of focal infection is found in gonococcal arthritis. The posterior urethra becomes infected, with a subacute or chronic infection in the prostate or seminal vesicles. From time to time a few gonococci escape from the focus in the genito-urinary tract and when conditions of susceptibility are right, the metastatic infection appears in the joints.

The problem of establishing the relation of focal infection to rheumatoid arthritis is more difficult because of the uncertainty which exists concerning the etiology. Indeed, in our opinion there is still considerable confusion in the clinical identification of this disease, and many cases of arthritis are still being classified as "rheumatoid" which do not belong in this category. Because of this confusion in classification it is difficult to compare the cases of so-called infectious arthritis noted at the Cornell Clinic with those to be discussed.

Clinical Study

The present study is based upon an analysis of 200 consecutive cases of typical rheumatoid arthritis. No case has been included that did not fulfill the classic pattern of the disease. For example, every case in the series showed, or had shown at some time previously, several characteristic fusiform fingers which, in our opinion, are a typical manifestation of this syn-

Table I

Cases Studied for Focal Infection

Foci	No. of Cases	Per cent
1. Definite foci		20
a. Tonsils	27	
b. Sinuses	11	
c. Teeth	2	
2. Doubtful foci		10
a. Tonsils	2	
b. Sinuses	11	
c. Teeth	11	
3. No demonstrable foci	140	70

drome. The sedimentation rate was accelerated in 93 per cent of these patients. The agglutination reaction with a strain of hemolytic streptococcus was strongly positive in 65 per cent.

In analysing these carefully studied cases we found definite evidence of infection in 20 per cent and a questionable focus in 10 per cent of the cases. We were surprised to find that 70 per cent of the patients revealed no demonstrable focus of infection. This high figure is in part explainable by the fact that the oral hygiene of these patients had been so carefully supervised before they came under our observation. Contrast this with the high incidence of focal infection found in the clinic patients 10 years ago!

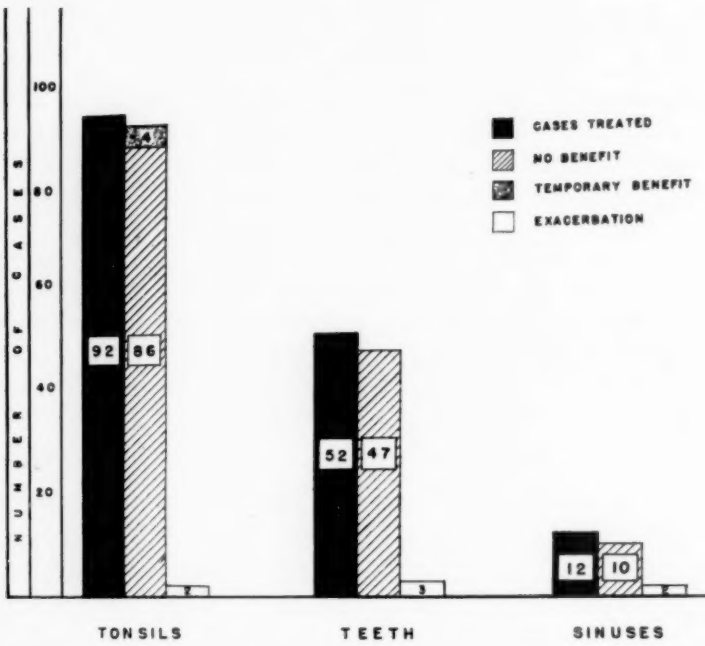

FIG. 1. The results of treatment of tonsils, teeth and sinuses in a group of 200 patients with rheumatoid arthritis.

Only 19 cases gave a history of an acute infection of the upper respiratory tract such as coryza, pharyngitis or influenza preceding the onset of the arthritis. A smaller number of cases came on after psychic trauma, childbirth, puerperal fever, physical injury or operation.

The focal infections which we have encountered in this series fall into two groups. The first includes those patients that gave a history of treatment of a focus of infection before they came under our observation. The second group includes the patients who, at the time when they were seen by us, had what was considered to be a focus of infection. It is obvious that we cannot state with certainty how many foci in the first group were sig-

nificant. However, it seemed of value to determine, if possible, the effect of removal of these foci upon the course of the disease.

The organ upon which the greatest attention had been "focused" was the readily accessible tonsil. The tonsils had been removed in 92, or 46 per cent, of the cases on account of arthritis although only about 15 per cent gave any history of tonsillitis or sore throat. The operation had no effect upon the course of the disease in 86 cases, and caused a severe exacerbation in two instances. There was temporary improvement in four cases. (Figure 1.) In no instance was the course of the disease arrested or the patient cured. In one instance the operation upon infected tonsillar stumps appears to have been the precipitating cause of the onset of the arthritis.

The problem of infection of the teeth and gums is a difficult one. Fifty-two patients had had some, and in many instances all, of their teeth extracted on account of arthritis. There was no benefit in 47 cases, and three patients reported a flare-up of the pain in their joints following tooth extraction.

The sinuses received less attention. Thirty cases gave a history of sinus disease, and 12 had been treated for sinusitis on account of arthritis before coming under our observation. The treatment was of no benefit in 10 cases and in two there was an exacerbation of the disease.

TABLE II

Results of Therapy

	Tonsils	Sinuses	Teeth
No. of cases with infection	27	11	3
No. treated for arthritis	20	5	3
No benefit	11	5	3
Benefit	7*	0	0
Exacerbation	2	0	0

* Temporary.

When first seen by us 27 patients had what was considered to be an infection of the tonsils or remaining tonsillar stumps. This diagnosis was confirmed in most instances by a rhinologist. Twenty of these cases were treated; 13 remained unimproved or became worse, and there was temporary improvement in only 7 cases. This improvement lasted from one week to several months.

At the time of examination only 11 of the 200 cases gave evidence of an active sinus infection. Five of these cases were treated, all without benefit.

The group of patients seen by us had exceptionally fine teeth, and most of them had had periodic dental examinations so that few infected teeth were found. In only three cases was additional dentistry performed. There was no benefit reported in any of these cases.

Other foci occurred in such small numbers that we have been unable to draw any conclusions as to their significance.

Experimental Study

The experiments of Krause, Willis [3, 4] and Freund [5] with tubercle bacilli, and more recently those of Angevine [6, 7] with hemolytic streptococci have shown that if bacteria are injected into a previously sensitized animal, they are fixed at the site of injection and show little tendency to disseminate from the original site. If this fact is applicable to foci of infection, one would expect little, if any, dissemination of bacteria from a well established focus.

It is apparent that no experimental work can parallel our clinical study since the etiology of rheumatoid arthritis is unknown, and the infecting agent in many of the foci is also unknown. However, since most writers believe that the tonsils, teeth and sinuses are usually infected with streptococci of various kinds, and less frequently with other organisms, the results of some experiments on rabbits to bring out the relation of focal infection to systemic disease may be of interest.

It is a well known fact that arthritis can be readily produced in rabbits by the intravenous injection of almost any strain of streptococcus. We have used a strain of hemolytic streptococcus which, when injected intravenously in small doses (2 c.c.) produced an arthritis in about 85 per cent of the injected animals. Arthritis appeared in one or more joints between the fourth and thirteenth day and often persisted for many months.

Using the same organism we have attempted to create foci at various selected sites. The dose of streptococcus was usually larger than that used for intravenous injection. In some animals single foci, and in others multiple foci were established. The following methods were used:

1. Suspensions of bacteria were injected into the following structures: the gum, sinus, prostate, testes, eye, pleural and peritoneal cavities, joint and skin.
2. Segments of the uterus and Fallopian tubes were isolated by ligature and injected with streptococci.
3. The renal pelvis was injected after ligation of the ureter.
4. The gall-bladder was injected after ligation of the cystic duct.
5. The animals in one group were fed large doses of streptococci over a considerable period of time.
6. Pledgets of cotton were soaked with streptococci and packed firmly into the nares where they remained for several weeks.

Blood cultures were taken in most animals at intervals of 1, 6, 24 and 48 hours after the infecting dose was given. Bacteria were usually not recovered from the blood after 48 hours. The results of these cultures gave us an indication as to how many microörganisms entered the circulation. By following the sedimentation rate and agglutination titer of the blood we were also able to obtain some evidence as to how long the focus of infection persisted. The greatest difficulty was to keep living organisms in a focus for any considerable length of time. The animals were watched

daily for the development of arthritis. They were occasionally killed when arthritis appeared but were kept in most instances for a period of two months. At the time of autopsy the focus was cultured to determine whether the injected organisms were still present; in most instances it was sterile. We were successful in establishing a focus in the eye so that we were able to recover organisms for as long as 30 days after a single intraocular injection. However, arthritis developed in only one instance in this group, and it appeared within six days.

Arthritis developed in only 11 of 100 rabbits. It was observed most frequently in those animals which had received injections into the gums, sinuses and male genitalia. The arthritis observed clinically was confirmed at autopsy by both gross and microscopic examination.

From these studies the following conclusions may be drawn:

1. Arthritis was produced in only 11 of 100 rabbits when injected by other than the intravenous route. To accomplish this it was necessary to use large doses of a suitable strain of streptococcus as well as a most susceptible animal.
2. Arthritis developed only in those animals from which streptococci were recovered from the blood stream shortly after injection.
3. In rabbits the gums were a particularly favorable site for the absorption of bacteria.
4. Repeated injections of bacteria caused no more arthritis than a single injection.
5. It was difficult to establish a chronic persistent focus of infection in rabbits.

Discussion

In our introductory remarks we stressed the popularity of the focal infection theory and how this popularity had led to its very wide application in the modern practice of medicine and surgery. Indeed, focal infection has become such a fetish that the specialist feels almost duty bound to discover a focus in his chosen field when the internist, in search of a diagnosis or an explanation for certain symptoms, turns to his specialized colleague for help. This is particularly true when we attack the problem of arthritis. How often in a particular case, the internist learns from the rhinologist that the antra or ethmoid cells show a slight increase of secretion and probably are the seat of a low-grade infection. If the internist goes further in his search, the urologist may report the prostate somewhat boggy with a few leukocytes and cocci in the expressed prostatic fluid. He suggests the possibility of a low-grade infection and perhaps recommends prostatic massage. When we turn to the oral surgeon, there may be still more uncertainty. "Several of the teeth have been devitalized, the gums are retracted, and there are changes in the periodontal membrane." The dentist suggests that

such teeth are a possible source of infection and probably should be extracted.

The reaction of the internist to these reports from specialists will vary according to his own platform concerning focal infection. If he is radical, he will have everything of an even suspicious nature removed. If he is conservative, he may ignore these reports completely and treat the patient instead of the focus.

The point we wish to stress, however, is that in the final analysis, these decisions should be made by the internist rather than by the specialist, and physicians should exercise a more conservative attitude regarding the treatment of tonsils, teeth and sinuses in rheumatoid arthritis than they have in the past.

The time has arrived for a complete revaluation of the focal infection theory. Undoubtedly there are cases of infectious arthritis which result from focal infection. However, as far as typical rheumatoid arthritis is concerned, it would appear from this study that chronic focal infection plays a comparatively unimportant rôle.

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CONCERNING THE DIFFERENTIATION BETWEEN BRONCHIAL ASTHMA VS. CARDIAC DISEASE, AND POSSIBLE ILL EFFECTS FROM THE ADMINISTRATION OF EXCESSIVE AMOUNTS OF EPINEPHRINE IN THE FORMER CONDITION *

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Cases of bronchial asthma are not infrequently encountered in which it is extremely difficult or perhaps even impossible to rule out a cardiac factor. Chronic bronchial asthma is invariably associated with varying degrees of emphysema. The latter results in permanent reduction of the vital capacity which, in some, may reach a low level. With a significant reduction of the vital capacity, shortness of breath appears on exertion, the venous pressure may be increased and occasionally dependent edema is observed. Moreover, the asthmatic attacks commonly occur more frequently and are often precipitated by exercise. Finally, it is generally agreed that the pulmonary manifestations of bronchial asthma may be indistinguishable from those of acute left ventricular failure (cardiac asthma). The following cases are illustrative of the types which present difficult problems in diagnosis:

Case Reports

Case 1. A man 55 years of age complained of shortness of breath on exertion and paroxysms of intense dyspnea. This patient had his first attack of asthma when 42 years old. During the preceding two years he had experienced shortness of breath on exertion. This had gradually progressed, and on a few occasions he had noted edema of the ankles. Sleep had become more and more difficult because of the frequent occurrence of paroxysmal dyspnea. It was obvious that this patient had advanced emphysema but it was impossible to exclude a cardiac factor because of some enlargement of the heart and changes in the electrocardiogram suggestive of coronary artery disease. The vital capacity while the patient was free from dyspnea, was 2 liters (57 per cent of the estimated normal) and 2.3 liters after the administration of epinephrine. Death occurred 18 months later after several weeks of cardiac failure involving particularly the right side of the heart.

At necropsy there was extensive dependent edema and passive congestion of the abdominal viscera. The lungs presented an advanced stage of emphysema. The heart weighed 510 gm. There was conspicuous hypertrophy and dilatation of the right ventricle and auricle with some involvement of the left side of the heart. The coronary arteries were relatively free from arteriosclerotic changes. Histological examination of sections of the myocardium showed small areas of fibrosis but only minimal changes in the coronary vessels.

Although this patient presented cardiac failure at the time of his death, the clinical manifestations, when first seen, no doubt were due to chronic pulmonary disease.

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Case 2. A man 58 years of age was admitted to the hospital because of cough and attacks of dyspnea. He had been subject to bronchitis for years and occasionally observed wheezing in the chest. There had been shortness of breath on exertion for several months. He had recently contracted an upper respiratory infection, and on two or three occasions had been awakened from sleep by intense dyspnea. Sibilant râles were heard throughout the chest. The vital capacity was 2.4 liters (60 per cent of the estimated normal). There was no demonstrable increase in the size of the heart. The cardiac tones were of good quality and the blood pressure was 120 mm. Hg systolic and 85 diastolic. The cardiac enlargement was verified by a teleoroentgenogram. The electrocardiogram did not reveal any significant alterations. The diagnosis was asthmatic bronchitis and emphysema.

Shortly following discharge from the hospital this patient began to notice more shortness of breath with routine physical activities and occasionally was conscious of heaviness or a squeezing sensation in the precordial region. A few weeks later he had a very severe attack of pain in the chest extending to the arms, accompanied by dyspnea so intense that morphine was required. He stated that the difficult breathing was quite similar to that experienced in the past. This patient has since had numerous attacks of paroxysmal dyspnea with wheezing in the chest, and now has advanced cardiac failure.

The age of this individual and the history naturally directed attention to the heart but the examination failed to reveal evidence of cardiac damage. In the light of the subsequent developments, however, one is inclined to question the correctness of the original diagnosis.

Case 3. A woman 61 years of age gave a history of having had hay fever, occasionally accompanied by asthma, for a period of years. She contracted a cold in November which persisted for about one month. Following this she was easily fatigued. The fatiguability later became more pronounced. The day after Christmas she felt unusually tired and had pain in the right hemithorax. Herpetic lesions subsequently developed. After recovering from the herpes zoster she developed another upper respiratory infection. Within a few days she began to notice shortness of breath, and later had an asthmatic-like attack. She remarked that she had never had asthma before except during hay fever season. This was fairly well controlled by the administration of ephedrine but continued to recur. Examination disclosed cyanosis, moderate enlargement of the heart, moist râles in the bases of the lungs, tenderness of the liver and edema of the ankles. Blood pressure was 190 mm. Hg systolic and 110 diastolic.

It is apparent that this patient presented both cardiac failure and asthma. The occurrence of the asthmatic attacks at this time is of particular interest and will be discussed later.

In 1929 Kountz, Alexander and Dowell [1] reported a series of 66 cases of pulmonary emphysema which simulated cardiac failure. Fifty-eight of these patients presented cyanosis and complained of shortness of breath on exertion. In 18 edema was present during the period of study whereas 21 gave only a history of this finding. In all, there was 39 (59 per cent) who either showed dependent edema or gave a history of it. The vital capacity was considerably reduced in all, and in some to less than 50 per cent of the estimated normal. Nine of these patients came to necropsy. In one there was hypertrophy and dilatation of both the right and left ventricle, whereas hearts of the remaining eight patients did not present significant pathological changes. Since, in eight there was no evidence of cardiac disease, it was necessary to explain the dyspnea, cyanosis and edema on another basis. It

was pointed out that the dyspnea and cyanosis might result from the reduced vital capacity. The edema was attributed to two possible factors, increased venous pressure and anoxemia. The problem was further studied by observing the effects of experimentally induced emphysema in dogs. Extensive emphysema was produced within a period of a few weeks by means of a ball-valve in the trachea. This procedure was carried out in a series of 16 dogs. Simultaneous determinations of the intrapleural and peripheral venous pressures were made at intervals for several weeks. It was observed that as the emphysema developed, intrapleural pressure rose and that this was followed by a rise of the venous pressure. These experiments seemed to provide a plausible explanation for the increase in the venous pressure but did not reproduce the dependent edema.

The experience of Alexander and his co-workers [1, 2] would seem to indicate that the incidence of cardiac damage in long standing bronchial asthma or in cases in which pulmonary emphysema is the dominant feature is relatively low. They concluded that the heart remains singularly free from injury after continuous bronchial asthma, despite the attendant emphysema.

In most cases of chronic bronchial asthma the heart is normal in size and the electrocardiogram does not reveal any important abnormalities. Under these circumstances one is ordinarily justified in concluding that the heart is not contributing to the pulmonary manifestations despite the presence of cyanosis and increased venous pressure. When, however, there is demonstrable cardiac damage, the evaluation of this is often extremely difficult. The response to digitalis and theophylline ethylenediamine may help solve the problem. Moreover, the results obtained by circulatory measurements such as carried out by Hitzig, King and Fishberg [3] and Oppenheimer and Hitzig [4] may provide important information. In the studies by Oppenheimer and Hitzig, dealing particularly with cases presenting advanced pulmonary disease, the circulation time from the arm to the lung was determined by the ether method, and that from the arm to the tongue by the use of saccharin or decholin. The circulation time from the lung to the tongue was obtained indirectly by subtracting the circulation time from the arm to the lung from that of the arm to the tongue. These tests were devised as means of determining the efficiency of the right and left ventricles. They are simple procedures and thus may be employed in routine practice. The normal circulation time from the arm to the lung ranges from 4 to 8 seconds. With frank right ventricular failure it may be extended to 12 seconds. The normal circulation time from the lung to the tongue is said to range from 4½ to 10 seconds. In cases of left ventricular failure, however, studied by Hitzig, King and Fishberg,[3] this time varied from 12 to 22 seconds.

One gets the impression from the literature that bronchial asthma and left ventricular failure rarely co-exist. Swineford and Magruder,[5] however, have recently reported 21 instances. All of their patients gave a

history of having had asthma in a mild form for several years and presented unmistakable evidence of cardiac disease. This study is of particular interest. It was undertaken primarily to determine the significance of wheezing in patients with paroxysmal dyspnea and evident cardiac disease. They pointed out that wheezing may or may not be present in acute left ventricular failure. This manifestation was regarded as a fundamental sign of bronchial asthma and therefore allergic in nature. With this in mind, the patients with cardiac disease and wheezing were carefully studied for allergic manifestations, and a high incidence was found. On the basis of these observations the theory was advanced that the addition of wheezing to paroxysmal dyspnea is, in the large majority of cases, an indication that the patient previously had had asthma of some degree, or that he was an allergic individual in whom the onset of the asthma is provoked by the pulmonary congestion incident to the failure of the left ventricle. This conception seems to provide a plausible explanation for the asthmatic aspect of acute left ventricular failure. Case 3 is illustrative of the type studied by Swineford and Magruder. It is to be recalled that until the onset of the cardiac failure, this patient never had asthma except during the hay fever season.

The types of cases under consideration bring up the question of the use of epinephrine. There seems to be a general feeling among the allergists that this drug may be given at frequent intervals and in large doses, if necessary, and over a long period of time without any apparent ill effects. Rackemann [6] states that he has had a number of patients who required 12 to 15 injections every 24 hours, for months at a stretch, and so far he had not observed any organic changes in these subjects. Coca [7] reports that the prolonged and excessive use of epinephrine has no lasting influence on blood pressure and produces no demonstrable organic changes. He also points out that even though large quantities may have been required to control the asthma, after several months of freedom from asthma, prompt relief may again be obtained from a small dose.

In many of the cases in which we have had difficulty in excluding a cardiac factor, the patients have received large quantities of epinephrine and yet their condition had gradually progressed, as indicated by the following patient:

This 68 year old man had asthma during early childhood until eight years of age. He then had no further trouble of this nature until the age of 65 when, following an upper respiratory infection, he was awakened from sleep by dyspnea. For several months thereafter the paroxysms of dyspnea occurred only at night. Later, however, they appeared during the day following exertion. The attacks gradually increased in frequency until they were coming every two or three hours. During the three months previous to admission to the hospital he had received six to eight injections of epinephrine during the 24 hours. This patient was having an asthmatic attack when admitted to the hospital and was promptly given an injection of epinephrine, but did not obtain any relief. He was quite cyanotic. The skin was moist and cold and the pulse was 130 per minute and of poor quality. There was moderate emphysema. The size of the heart was difficult to determine, but a

roentgenogram taken later showed it to be slightly increased. There was a gallop rhythm. The blood pressure was 180 mm. Hg systolic and 110 diastolic. An electrocardiogram showed a negative T deflection in Leads II and III. Morphine was then prescribed and the patient had a fairly good night. Thereafter the attacks were controlled by the administration of a solution of 50 per cent glucose with 0.48 gm. of theophylline ethylenediamine. The effects of the medication were noticed by the patient soon after the solution was introduced into the vein and complete relief was obtained ordinarily within five minutes. After two weeks, the vital capacity had increased from 1 to 3.2 liters and the patient stated that he could breathe more easily than at any time in three years. Similar results from the use of glucose solution with theophylline ethylenediamine have been observed repeatedly in patients who have been receiving large quantities of epinephrine.

There are reasons for believing that the function of the heart may be impaired by the therapeutic use of excessive amounts of epinephrine, as suggested by the above case. Myocardial lesions have been produced repeatedly in rabbits by the intravenous injection of epinephrine.[8, 9] In the earlier experiments, a series of injections was employed. In certain instances, as pointed out by Pearce,[8] death occurred from acute dilatation of the heart and pulmonary edema within a few minutes following the initial injection of 0.2 c.c. of 1 to 1000 solution of epinephrine. Fleisher and Loeb,[10] and others,[11] have since shown that changes in the myocardium occur very frequently in animals following a single injection of the above amounts of epinephrine.

The action of epinephrine on the coronary vessels has been extensively studied. On the whole, the results have been very conflicting, but certain experiments seem to produce convincing evidence that there is a constricting effect.[12] This is further supported by the electrocardiographic changes induced in animals by the injection of epinephrine. In experiments recently reported by Milles and Smith[13] and by Douglas, Gilfand and Shookhoff,[14] pronounced alterations were observed in the T deflection and the S–T segments. Furthermore, Douglas and his co-workers were able to abolish this effect by the administration of nitroglycerine.

Levine, Ernstene and Jacobson[15] have shown that the subcutaneous administration of epinephrine in doses of 1 c.c. frequently precipitates attacks in patients with angina pectoris. While it was suggested that this drug might be employed as a diagnostic test in questionable cases, it was pointed out that it should be used very cautiously. Other observers have since called attention to the possible ill effects from the administration of epinephrine in cases of coronary artery disease. Katz, Hamburger, and Lev[16] have studied the effects of an injection of 1 c.c. of a 1 to 1000 solution of epinephrine on the electrocardiogram of normal persons and patients with angina pectoris. They reported a downward deviation of the S–T segment and a reduction in the amplitude of the T-wave.

Finally, the action of theophylline ethylenediamine is of interest in this connection. This drug is commonly prescribed because of its action on the coronary vessels and is one of the most effective remedies in the treatment

of acute left ventricular failure.[17] It also has a favorable effect on the bronchial obstruction in asthma.[18] Moreover, it has been employed with success in patients who fail to respond to epinephrine,[19, 20] as illustrated by the case previously cited. Herrmann and Aynesworth[21] have recently reported 16 cases in which theophylline ethylenediamine had been administered as an emergency measure after epinephrine had failed to give relief. They state that prompt, complete and persistent relief was obtained from 31 of the 41 injections given under these circumstances. It was furthermore pointed out that after treatment with theophylline ethylenediamine, the usual response to epinephrine was restored.

Summary

The differentiation between bronchial asthma and cardiac disease not infrequently presents a difficult problem. This pertains particularly to certain of the cases with a long history of asthma and significant emphysema who have reached the age in which degenerative disease of the heart is prevalent, to those in whom the onset of the asthma occurs late in life, and to those with both chronic pulmonary disease and cardiac disease. Cases illustrating each of these groups are cited. Finally, it is suggested that the excessive use of epinephrine may impair the function of the heart.

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THE TREATMENT OF LIVER DISEASE *

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Introduction

Attempts at treatment of parenchymatous disease of the liver other than those types which are entirely self-limited constitute a somewhat discouraging chapter in medical history. Most therapeutic procedures have been used, discarded, and readopted at intervals over a period of many years and all have failed so signally to cure or control such diseases that the present generally pessimistic attitude in regard to therapeusis is well justified. However, within recent years a great deal of valuable experimental work has been done on the pathologic physiology of the liver, indicating the tremendous reserve function of the organ and its capacity for regeneration and repair. On the basis of such observations it would seem at least theoretically possible to make a better record in treatment. The material to be presented here is not so much a record of therapeutic triumphs as it is an attempt to review recent work which holds promise of therapeutic helpfulness in cases of disease of the liver and to cite its possible clinical application.

For purposes of the discussion to follow, a definition of the conditions to be discussed seems desirable. The term "hepatic disease" as it is used hereinafter refers to chronic destructive and degenerative processes involving the parenchyma of the liver. Simple atrophy, fatty metamorphosis, and focal necrosis, either confined to the region of the central vein of the lobule or affecting the entire structure, apparently represent the fundamental lesions associated with all types of hepatic injury, whether this may be caused by biliary obstruction, infectious diseases or specific hepatotoxic agents, in that the destruction, subsequent repair, and regeneration of the liver proceed in about the same manner although not necessarily at the same rate. For instance, one may see pathologic evidence of acute atrophy of the parenchyma of the liver following calculous obstruction or stricture of the common bile duct; it may occur postoperatively after removal of the gall-bladder [1]; it may be a feature of thyrotoxic crises or it may follow the use of certain hepatotoxic drugs. Finally, chronic atrophy (cirrhosis) may develop on the basis of repeated episodes of acute injury of the liver. There is, then, good pathologic evidence for the unity of most primary injuries of the liver, a point of view first held by Legg.[2] On both clinical and experimental ground it may be said also that the general problem of protecting the parenchyma of the liver is somewhat the same in treatment of all types of hepatic injury.

There may be mentioned here some general factors which influence the

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course of hepatic injury. It has been shown that the liver neither regenerates nor repairs itself in the presence of complete obstruction of the bile ducts [3]; similarly, regeneration does not occur if a hepatotoxic agent is still operative or if there is a marked reduction of flow of portal blood. The first and second factors, of course, can be corrected in some instances although the third remains beyond present methods of control. However, it is believed that compensatory changes in the circulation occur in the course of time which minimize this difficulty to some extent.

Dietary Factors

Since the early experience of Opie and Alford [4] on the effects of diet on the course of hepatic injury following experimental poisoning by chloroform and phosphorus it has been known that a high intake of carbohydrate has a definite specific protective effect against hepatic necrosis. This observation has been substantiated many times in a variety of experimental hepatic lesions and, on the basis of such observations, a dietary regimen for all types of hepatic disease has been agreed on generally. The usual practice is to give a diet containing 350 gm. or more of carbohydrate, 1 to 1.5 gm. of protein for each kilogram of body weight, and an amount of fat compatible with the patient's tolerance and caloric requirements. Administration of additional carbohydrate in the form of syrups, jellies, jams, candy, and sweetened fruit juice also is encouraged. The difficulties in the administration of such a diet to seriously ill patients is obvious and, for this reason, additional amounts of carbohydrate in the form of glucose must be administered intravenously. The use of glucose will be discussed in a subsequent section of the paper; at this time it suffices to say that there is no apparent great advantage in giving glucose by vein if the patient can take adequate amounts of carbohydrate by mouth.

It has been demonstrated experimentally that the liver maintains a reasonably adequate function even on diets of widely varying composition, even under circumstances when the content of glycogen is low and fatty change is microscopically evident. In other words, the diet, at least so far as the chemical composition of the liver is concerned, may be varied somewhat without loss of therapeutic effect. It is apparent, however, from studies on animals and patients that the success or failure of treatment of a patient who has a severely damaged liver depends to a large extent on the patient's ability to continue to take a well balanced and ample diet over a long period.

The use of concentrates of vitamins in connection with dietary treatment is discussed in a later paragraph but some reference to the subject is essential at this point. The liver is known to be instrumental in the formation or storage of vitamins A, B_1, the B_2 complex, C, and D; these functions, in all probability, must be disturbed considerably by injury to its parenchyma. If bile is diverted from the intestinal tract by an external

fistula or by mechanical obstruction of the common duct, the adsorption of vitamins also is affected adversely. No doubt, the reduced production of bile acids which is so apparent in experimental hepatic injury and which probably occurs with clinical hepatic disease, has a similar effect but it is less marked than that caused by diversion of bile. Greaves and Schmidt [5, 6] have shown that, in the presence of experimental biliary fistula, vitamins B and E as well as certain substances necessary for coagulation of the blood, are not absorbed. Heymann [7] has demonstrated similarly a failure to absorb vitamin D in the presence of biliary obstruction and also has found that very large doses of this vitamin are necessary to maintain rachitic rats poisoned by carbon tetrachloride. Difficulties in the absorption, storage, and utilization of vitamins thus may be an element of great importance in the progression of hepatic disease. Eppinger [8] has recognized these difficulties of absorption and has recommended that vitamins be administered only by injection under these circumstances. Possibly with large dosage and the judicious use of bile or bile salts, this may not be necessary but, in any case, the addition of concentrates of vitamins to the diet seems essential.

Specific Substances Which May Protect the Liver

It has been assumed that one effect of the forced administration of a high intake of carbohydrate is reduction of the content of fat of the diseased liver, at the same time favoring the deposition of glycogen. This appears to have been accomplished among experimental animals but it is difficult to prove that such a reciprocal relation is demonstrable among human subjects. Various special measures have been advocated to assist in reducing the content of fat of the liver and, on the basis of the well known observations of Allan and his coworkers,[9] and of Best and others [10, 11] on pancreatectomized dogs, derivatives of lecithin and choline have been advocated as essential additions to the diet in treatment. The hormone "lipocaic" which Dragstedt and his coworkers [12] have isolated from the pancreas, has also been shown experimentally to exert a definite effect on the content of fat of the liver after pancreatectomy. Comfort and I [13] have shown definite clinical effects among certain patients who had pancreatic atrophy and, presumably, fatty livers from the use of this substance; notably the disappearance of ascites and edema and reduction in the size of the liver. Its use among patients who have fatty metamorphosis of the liver from other causes has been hardly more than considered but there is a theoretical basis for believing that it may be effective.

The recent studies of Neale and his collaborators [14–17] on the effect of various purine derivatives in protecting the liver against experimental injury have attracted much deserved attention. These investigators have shown that sodium xanthine and xanthine, both in the naturally occurring and synthetic forms, will protect the liver of animals against lethal doses of carbon tetrachloride or chloroform. Unfortunately, no definite effect has

been observed in these animals if the purine derivatives are given after the hepatotoxic agent has been administered. Clinical studies have not been reported as yet but certainly the subject holds much promise for further study. It is of interest to note that patients with gout, who may have difficulty in metabolizing the xanthine bases, rarely develop liver atrophy from cinchophen; perhaps the retained xanthine derivatives may exert their protective influence in such cases.

The Nature of Hepatic Insufficiency

Various circumstances which may arise in the course of parenchymatous injury of the liver obviously require special therapeutic measures. Of these, the most serious is hepatic insufficiency. Like its counterpart, the uremic state, its nature is not well understood. It differs widely from the syndrome produced by total hepatectomy; hypoglycemia is rare, although it is possible to show minor disturbances of carbohydrate metabolism by appropriate functional tests. It has been possible, in a few instances, to demonstrate some failure in deaminization and, rarely, an elevated concentration of uric acid in the blood has been noted. Fatty change in the liver, often a feature of acute forms of atrophy of the liver, may be suggested by a very high concentration of fats in the blood; more frequently, however, the lipid substances of the blood may decrease to low levels and the cholesterol esters may virtually disappear.[18] The excretory functions, particularly in respect to dyes and bilirubin, always are impaired, but this fact may not be as significant as first was supposed. None of the disturbances in metabolism mentioned above are necessarily serious or fatal; in other words, we must look elsewhere for the mechanism by which hepatic failure causes death. The clinical syndrome itself often suggests acute intoxication and it has been suggested that perhaps hepatic insufficiency represents failure of normal processes of detoxification.[19] The liver is probably the first line of defense against many endogenous and exogenous toxins; when its functions in this respect fail, the load falls on the kidneys with resulting renal insufficiency. Although complete proof of this hypothesis is lacking it is justifiable, tentatively to assume that the syndrome of "hepatic insufficiency" is fundamentally dependent on a failure of the mechanism of detoxification.

The known chemical changes of the blood in cases of experimental and clinical hepatic insufficiency may be stated briefly. Soffer and his collaborators[20] studying dogs poisoned with large doses of arsphenamine, have found a consistent hemoconcentration among these animals, with an associated fall in the concentration of chlorides of the plasma, the development of acidosis, and an increased content of lactic acid in the blood. Chemical changes in the blood of the degree described are seen very rarely among human subjects, although some concentration of the blood and hypochloremia may occur in the occasional case. The reason for this disturbance in the

metabolism of the chloride is not clear; Beckmann [21] has suggested that the liver may retain chloride in the capacity of a storage reservoir. The possibility of the liver exerting some hormonal influence on chlorides also has been considered.[22] Elevation of the concentration of urea of the blood and nonprotein nitrogen are late developments and, presumably, depend on renal failure rather than on primary hepatic insufficiency. Acidosis, as shown by low carbon dioxide combining power and even by changes in the pH of serum has been observed clinically and elevation of the concentration of lactic acid of the blood comparable to that encountered among Soffer's animals also has been noted.[23] Gautier and his collaborators [24] have described an almost identical change in the blood chemistry of a human subject accidentally poisoned with carbon tetrachloride. Anoxemia [25] also has been described, a phenomenon which may be of some importance. McMichael [26] and others [27, 28] have demonstrated the sensitivity of the liver to oxygen lack and its rather peculiar vulnerability in this respect because of its unusual blood supply. The nature of the anoxemia in hepatic disease has been discussed by Keys and me [29]; it appears to depend on a decrease in affinity of hemoglobin for oxygen as shown by displacement of the oxygen dissociation curve to the right. Whether this can be attributed to some fundamental peculiarity of the hemoglobin or to the admixture of other substances in the blood interfering with normal respiration as yet is undetermined.

Treatment of Hepatic Insufficiency

Management of hepatic insufficiency depends primarily on the maintenance of an adequate intake of carbohydrate, the administration of sufficient quantities of fluid to dilute and to eliminate toxins, and the correction of hypoglycemia, anoxemia or hemoconcentration, if these happen to be features of the case under consideration. The intake of carbohydrate, as a rule, can be maintained in such cases only by the persistent daily intravenous administration of glucose. Experimentally, Althausen and Stockholm [30] have been able to demonstrate that little glycogen is formed by the liver after intravenous administration of glucose when lethal intoxication is present but, in the presence of sublethal intoxication formation of glycogen proceeds at a more satisfactory rate when glucose is given by vein than when equal amounts are given by mouth.

Glucose therapy, although not spectacular, is extremely valuable; Jones' [31] figures indicate that among individuals who have hepatic insufficiency and who have received glucose intravenously for a period of ten days or longer, the mortality rate is only 22 per cent. In view of the fact that hepatic insufficiency has been regarded as an almost invariably fatal condition, these results are most encouraging. The amount of glucose to be administered depends on whether or not the patient is able to take food by mouth. From 1 to 3 liters of a solution of 5 to 10 per cent glucose can and should be ad-

ministered daily and in some cases even larger amounts have been given by continuous venoclysis.

So far as other abnormal chemical conditions of the blood are concerned, hemoconcentration usually is corrected by administration of fluids in the manner described. If the chlorides of the plasma are low in concentration it is a relatively simple matter to administer additional sodium chloride along with the glucose. There are, however, cases in which administration in this manner has had little effect on the level of chloride present in the blood. In one such case recently observed, the use of suprarenal cortical hormone, which is known to produce retention of salt even when no suprarenal cortical insufficiency is present,[32, 33] brought the concentration of chlorides of the blood up to normal. It is important to maintain the concentration of hemoglobin at a normal level so far as possible, a matter which may require repeated small transfusions. Correction of the anoxemia is assisted materially by such transfusions, both the oxygen capacity and the percentage of oxygen saturation of hemoglobin in arterial blood being definitely elevated by the addition of normal blood.[34] In the exceptional case associated with marked cyanosis and hyperpnea, oxygen therapy in some form may be valuable.

Treatment of Ascites and Edema

The presence of these complications in so many instances of chronic atrophy (cirrhosis) of the liver has attracted attention since the time of Laennec and treatment often has been concentrated on the ascites to the detriment of the patient. Treatment with diuretics and purges has been favored especially in the past and, in fact, the methods employed often have been essentially those used in the treatment of cardiac decompensation. This preoccupation with the problem of transudation becomes justifiable if the disability produced by such conditions is considered and if it is realized that the disappearance of ascites is often synchronous with improvement.

Considerable data have been accumulated recently on the mechanics of transudation associated with hepatic disease which have changed the therapeutic approach to the problem to a great extent. Stasis in the portal venous system formerly has been held to be the principal factor in the formation of ascites, although experimental evidence to substantiate this view has been lacking. Actually, portal venous pressures never have been measured directly, although on anatomic grounds alone, it is reasonable to suppose that portal venous hypertension exists in the presence of a cirrhotic liver. The best available estimations of such pressures are those of Thompson and his collaborators[35] and McIndoe.[36] The investigators first mentioned, measured pressures directly in the splenic vein in the presence of Banti's disease and in one case of schistosomiasis and splenomegaly; the averages for both cases were about 375 mm. of water. McIndoe perfused cirrhotic livers removed at necropsy and found that a pressure of 20 to 30

mm. of mercury (260 to 390 mm. water) was required to force fluid through the portal venous bed. These represent large increases because normal portal vein pressures probably do not exceed 125 mm. of water. Such elevated pressures existing in the portal venous system, of course are to be balanced against the colloidal osmotic pressure exerted by the proteins of the serum. It has been assumed that the colloidal osmotic pressure is reduced in patients who have cirrhosis, by virtue of the hypoproteinemia and reversed albumin-globulin ratio which seem to characterize this condition. The reasons for this disturbance in concentration of the proteins of the plasma have been discussed elsewhere [25, 37] and will not be considered here. The extent of this reduction of colloidal osmotic pressure dependent on hypoproteinemia has been computed from various formulas but its actual magnitude has not been appreciated until relatively recently. Recent figures [38] indicate that, in the presence of chronic injury of the liver, the colloidal osmotic pressure of the serum may be reduced as much as 50 per cent from a normal level of about 372 mm. of water. This rather remarkable decrease cannot be correlated satisfactorily with values for total protein although there is much better correlation with figures for serum albumin. In cases of cirrhosis, therefore, the usual balance between hydrostatic pressure in the portal venous system and colloidal osmotic pressure of the serum is greatly disturbed in a direction which favors transudation.

Such simple pressure relationships, however, probably are not the only factors in the problem; a third variable must be considered. It has been assumed for years that some injury to serosal surfaces may exist in cases of hepatic disease; in fact Eppinger has spoken of "Seröse Entzündung" with increased permeability of such surfaces as the pleura and peritoneum. Among animals whose livers have been rendered cirrhotic by carbon tetrachloride and which have been subjected further to plasmapheresis in order to reduce the concentration of proteins of the plasma, Bollman [39] has found no evidence of a constant "edema level" as measured by determining osmotic pressures. Both observations, of course, argue for the existence of a third factor, that of increased permeability of capillaries and membranes. It is suggested that the "permeability vitamin" recently isolated by Szent-Györgyi [40] may be the determining factor in our equation. This material, a flavone glucoside, is present in citrus fruits and is allied closely to vitamin C; if it is stored in the same manner as vitamin C, it is reasonable to suppose that it may be affected by pathologic change in the liver.

On the basis of the above-mentioned evidence the logical treatment of ascites and edema, therefore, would be directed toward (1) improvement of the condition of the liver, a matter which has been discussed, (2) decrease of portal venous pressure, and (3) elevation of the concentration of proteins of the plasma thereby increasing the colloidal osmotic pressure of the serum. The first requirement can be met only by some surgical procedure, of which the Talma-Morison omentopexy is a fair example. General surgical experience, as cited by various authorities,[41-43] has been

somewhat disappointing with this procedure and it cannot be recommended wholeheartedly. The heroic process of partial enterectomy as performed by Fuller and her collaborators [44] may serve its purpose by reduction of portal venous flow, but, possibly, reduction of the area of serous surface through which transudation can occur is equally important.

Attempts to elevate the concentration of proteins in the plasma offer a considerably greater prospect of success than omentopexy or partial enterectomy. Centurion [45] attempted to accomplish this by reinjecting ascitic fluid and, by virtue of the content of albumin of this material, occasionally achieved the desired effect. Routte's operation,[46] that of permanently draining the ascitic fluid into the proximal end of the saphenous vein (veno-peritoneostomy) has been employed with reported good results. Both of these rather formidable measures obviously should be deferred until an attempt has been made to elevate the osmotic pressure of the patient's serum by less spectacular means. For obvious reasons, a relatively high dietary intake of protein is believed to be desirable. Transfusions of whole blood and plasma have a temporarily beneficial effect because of the additional normal albumin which they supply. The use of substitutes for blood such as solution of acacia also has been tried with somewhat encouraging results; as Kerkhof,[47] and Butt and Keys [48] recently have shown, concentrated solution of acacia raises the osmotic pressure of serum in vitro and in vivo and, in some instances, has produced diuresis among patients who have hypoproteinemia. Similar effects, but on a smaller scale, have been noted among patients who have hepatic disease. An injection of 500 c.c. of a solution of 6 per cent acacia on three consecutive days frequently will produce a temporary rise in osmotic pressure of approximately 20 per cent, a change sufficiently great to retard the rate of accumulation of fluid. Large doses must be used with caution since they may produce hepatic damage and depress the total protein still further. Acacia, of course, is eliminated slowly from the blood stream and it is sometimes necessary to repeat its administration to secure the desired effect.

In addition to the measures mentioned above the effect of vitamins on the proteins of the plasma may be considered. Field [49] has produced evidence to show that vitamin B complex given parenterally in large doses may elevate the concentration of proteins of the plasma and retard transudation even when such a rise in concentration is not large. Patek [50] has recommended independently a combined attack with all available concentrates of vitamins; he advises that the patients be given, daily in addition to the diet mentioned in an earlier paragraph, 30 minims of Oleum Percomorphum, 12 ounces of orange juice, 2 ounces of Valentine's Liver Extract, 3 drams of Vegex and parenteral crystalline vitamin B_1, the latter being intravenously injected daily in doses varying between 4 and 10 mg. His results in a selected group of cases have been very encouraging. The practice of feeding of concentrates of vitamins together with a diet high in carbohydrate and protein to patients who have cirrhosis has been followed at The Mayo Clinic

for some months and strikingly good responses have been noted in some cases. As has been stated, patients who are able to eat a liberal diet invariably make better progress than those who have anorexia and, certainly, attempts at forced feeding and the use of concentrates of vitamins have much to recommend them on this basis alone.

Intramuscular injections of liver extract may also have some direct effect on nitrogen balance and on the retention of protein. In cases of pernicious anemia, the use of liver extract will produce a positive nitrogen balance [51] and, apparently it has somewhat the same effect in cases of hepatic disease although on a much smaller scale. As Heath and Taylor [52] have shown, hemoglobin is formed first in response to the stimulation of liver fractions and this formation may continue even at the expense of the protein of the plasma and tissues. If the patient's dietary intake of nitrogen is sufficiently large, more nitrogen may be retained and, under such circumstances, it is conceivable that a rise in the concentration of protein of the plasma might occur. Studies on the metabolism of nitrogen in cases of liver disease, when made on edematous patients who had capricious appetites, are difficult to interpret but, in at least two instances, evidence has been obtained which indicates a strongly positive nitrogen balance after administration of large doses of liver extract parenterally. In these experiments, elevation of the concentration of proteins of the plasma was not sufficiently great to be worthy of comment but there appeared to be definite clinical improvement and a reduction in the rate of transudation.

The use of mixtures of amino acids intravenously eventually may help to solve the problem of hypoproteinemia. Elman [53, 54] has shown that a mixture of amino acids obtained from hydrolized casein, fortified with cystine and tryptophane, has produced definite retention of nitrogen among dogs after plasmapheresis. Further therapeutic tests with mixtures of amino acids among patients who have hypoproteinemia must be performed before any definite statements can be made as to the efficacy of amino acids in treatment.

In concluding this discussion of ascites and edema, some reference to the time-honored use of diuretics is essential. The acid-producing salts and the mercurial diuretics which were in vogue ten years ago are less popular today, because a striking diuretic response appears to be difficult to obtain among a majority of patients who have damaged livers. Diuretics may be ineffective early in the course of treatment and produce good results later when the patient's general condition (and presumably the state of the parenchyma of the liver) has improved. Diuretic treatment, however, never should be forced; trial of potassium or ammonium salts for a few days followed by one or more doses of the injectible mercurial diuretics should be sufficient to determine whether or not the patient in question will respond favorably. If a good increase in the volume of urine is not obtained by this means, diuretics should be omitted; forced administration has been known, on many occasions, to lead to the development of fatal hepatic and renal insufficiency.

Tapping entails far less risk and, as Osler [55, 56] noted, may be resorted to frequently without greatly affecting the general condition of the patient. White's [57] frequently quoted observations on the usual fatal termination of portal cirrhosis after tapping, certainly do not hold at the present time.

The Anemia of Liver Disease

Macrocytic anemia which is a frequent finding in all instances of advanced or chronic hepatic injury [58] is not particularly responsive to treatment. The anemia itself is supposedly dependent on failure of the liver to store the active hematopoietic principle or on its inability to present it to the body in a proper form for utilization.[59] This difficulty in utilization is apparently of considerable importance, because long-continued and persistent treatment with large dosages of active fractions of liver is required to produce any particular effect on the blood. Frequent transfusions and the intermittent administration of iron in some form are necessary adjuvants to treatment, particularly in the seriously ill patient whose intake of food is limited.

Hemorrhage in Liver Disease

Hemorrhage associated with disease of the liver may assume two distinct forms: (1) that which results from rupture of collateral circulatory channels, and (2) that which is dependent on some intrinsic change in the coagulating properties of the blood. The control of the first situation, which ordinarily is represented by bleeding from esophageal varices, should be regarded as a surgical problem. Splenectomy is helpful in the treatment of hemorrhage which characterizes Banti's disease, achieving its effects partly by the reduction of the circulatory load on the portal system and partly because the operation cuts off one large contributing source of blood to the esophageal varices coming through the *vasa brevia* of the spleen. Unfortunately, the procedure is not feasible in most instances of primary cirrhosis because of the risk involved. Direct ligation of the coronary veins of the stomach [60] has been attempted as a means of controlling bleeding from collateral channels; although it is technically difficult and is subject to certain definite limitations, it may be considered in certain cases after ordinary palliative measures have failed.

So-called "cholemic" bleeding has been, for years, an unsolved problem. The nature of the coagulation defect has been, until lately, an unsettled question and methods of treatment have been largely empirical. Deficiencies of calcium have been postulated and, also it has been suggested that various sulphydryl [61] anticoagulants may be present in jaundiced blood. The most recent evidence on the subject indicates that neither of these theories is correct. Quick [62] was the first to note that the deficiency was probably of the prothrombin of the blood, all other elements necessary for coagulation being present in normal amounts. This observation has been

corroborated by numerous workers and it may be regarded as an established fact.

A good deal of further information about deficiency of prothrombin has been forthcoming in recent months and has revealed the existence of three widely varied conditions associated with such a shortage. Hawkins and Brinkhous,[63] in studying the hemorrhagic state induced by complete biliary fistula in dogs, have noted a deficiency of prothrombin and showed that it could be corrected by the feeding of bile. Apparently, therefore, one factor necessary for the maintenance of a normal level of prothrombin is the presence of bile in the bowel.

A second factor was pointed out much earlier by the pioneer studies of Dam and his coworkers.[64-68] They demonstrated that internal, subcutaneous, and intramuscular hemorrhages developed among chicks fed on a diet deficient in certain fat soluble compounds, but adequate in respect to vitamins A, B_1, B_2, C and D and total fat and cholesterol. This bleeding is associated with, and apparently is attributable to, a decrease in the concentration of prothrombin of the blood. The hemorrhagic tendency, as Dam [66] first showed, is cured promptly by administering a substance found in the unsaponifiable, nonsterol fraction of hog-liver fat and in alfalfa. This is the substance which has been designated tentatively as vitamin K (Koagulations-Vitamin).

Thus, there are two factors, the presence of bile in the bowel and a hypothetical fat soluble vitamin, which are known to be of importance in maintaining a normal level of prothrombin. A third and equally important factor remains to be considered. A marked hemorrhagic tendency exists among animals fed spoiled sweet clover hay and, as Roderick [69] and later, Quick [62] showed, this also depends on a deficiency in prothrombin. The condition is relieved by transfusion of blood and by feeding alfalfa, which is protective in concentrations as low as 5 per cent of the total diet. Quick concluded that some toxic factor present in spoiled sweet clover hay depleted the supply of prothrombin and that an exogenous supply of some unknown material was required for its repletion. Just how spoiled sweet clover affects the normal store of prothrombin is not known. Possibly the parenchyma of the liver is affected since Roderick [70] demonstrated focal necrosis of the liver in some animals dying from toxic sweet clover disease. This possibility is supported by the recently published studies of Warner, Brinkhous and Smith [71] who showed that, in cases of experimental chloroform intoxication, a deficiency in both fibrinogen and prothrombin occurred. By varying the dose of chloroform, deficiency in prothrombin alone could be produced and the fibrinogen was left virtually unaltered. Their data appeared to indicate that the liver is concerned in the manufacture of prothrombin. It seems justifiable then, to conclude that: 1. The hemorrhagic state associated with disease of the liver is attributable to a deficiency of prothrombin which, in turn, is attributable to failure of absorption or utilization of some substance normally present in the diet which required bile for

its absorption. 2. This substance may be the hypothetical coagulation vitamin (vitamin K). 3. Additional "toxic" factors may deplete the supply of prothrombin, as occurs in cases of sweet clover disease and necrosis of the liver caused by chloroform.

From a clinical standpoint, administration of extracts containing vitamin K together with bile or bile salts to patients who have jaundice has rapidly reduced an elevated prothrombin time to a point within normal limits and, in certain cases, has prevented hemorrhage or has had a definite inhibitory effect on actual bleeding. Administration of bile alone to an individual who was ingesting an adequate diet has resulted in a shortening of the increased prothrombin time. Administration of vitamin K alone, when bile is absent from the intestinal tract, has had little or no effect in decreasing the elevated prothrombin time of one individual.

The results obtained thus far encourage the belief that prevention and control of the hemorrhagic diathesis among patients who have obstructive jaundice or primary injury of the liver may be accomplished by administration of bile and concentrates of vitamin K. Warner, Brinkhous and Smith at the University of Iowa have obtained independently results which confirm this impression.*

The application of some of these methods of treatment to specific cases may be illustrated best by a brief report of two cases. The first pertains to the management of a case of hepatic insufficiency associated with the ascitic stage of cirrhosis; the second, to the problem of cholemic bleeding.

Case Reports

Case 1. A man, aged 47 years, was admitted to the hospital, giving a history of jaundice, ascites, and edema of six weeks' duration. There was a long history of alcoholism, and hepatic enlargement had been noted by the patient's physician more than a year previous to admission here. Prior to the development of icterus he had lost some weight and had bled from the nose and gums. On physical examination, the striking findings were slight cyanosis, jaundice, anasarca, and malnutrition; there was some glossitis and the breath had a "mousy" odor. The size of the liver and spleen could not be determined because of the large amount of fluid present in the abdomen. Laboratory studies revealed marked macrocytic anemia, the concentration of bilirubin was 3 mg. per 100 c.c. of serum, and retention of bromsulphalein was present grade 3 (on a basis of 1 to 4); the total concentration of proteins of the plasma was normal (6.7 gm.) but the albumin-globulin ratio was 0.45 and the colloidal osmotic pressure was 200 mm. of water. The clinical diagnosis was portal cirrhosis with impending hepatic insufficiency.

Paracentesis was performed two days, 10 days, and one month after admission, respectively and two small transfusions (250 c.c.) were given in the first month the patient was in the hospital. Because of an inadequate intake of food, glucose was given intravenously (1 liter of a 10 per cent solution) daily for five weeks.

* Since this paper was written a personal communication from Dam and Glavind has been received. They have published preliminary reports (Vitamin K I Den Menneskelige Patologie. Saertryk af Ugeskrift für Laeger, No. 10 pp. 248–255, 1938; and Vitamin K in human pathology, Lancet, 1938, ccxxxiv, 720–721) which are in agreement with the hypothesis of prothrombin deficiency as a cause for hemorrhage in jaundiced patients. They have also prepared an emulsion of spinach, containing vitamin K which reduces the coagulation time of blood on intramuscular injection.

Brewers' yeast, iron, and cevitamic acid were given in full doses. Diuretics were tried cautiously and proved ineffective. One month after admission, 1500 c.c. of a solution of 6 per cent acacia was given in three equal and divided doses on successive days; the colloidal osmotic pressure rose about 30 mm. of water and gradually fell off; some increase in the output of urine was apparent and the rate of accumulation of fluid was never such as to require tapping thereafter. At about this time, intramuscular injections of liver extract were begun and 25 doses (1 c.c. each) of a concentrated preparation was given in the next six weeks; the anemia was corrected very slowly and neither the concentration of proteins of the plasma nor the osmotic pressure of the serum was affected greatly. Three transfusions of blood (500 c.c. each) also were given in this period. In spite of the apparent lack of improvement in the concentration of the proteins of the blood, the appetite gradually increased and the ascites and edema slowly disappeared. Eighty-four days after admission the patient was dismissed free of jaundice and anasarca, with a virtually normal number of erythrocytes. The liver and spleen were just palpable but retention of dye persisted. His physician at home reported that the patient was well and in good condition six months later and there had been no recurrence of his symptoms after one year.

In reviewing this patient's clinical course the most remarkable feature was the very gradual improvement with almost complete lack of any periods of spectacular improvement. The lesson to be learned is, of course, that persistence may accomplish much in the rehabilitation of these patients and that eventual recovery depends on restoration of normal hepatic function rather than on elimination of any one feature of the syndrome associated with this disease. Obviously, this is a slow process, but the results, once attained, are eminently satisfactory. We have records of several similar cases, some of which were not attributable to the use of alcohol or other hepatotoxins.

Case 2. The control of bleeding presents a somewhat more dramatic situation, one in which prophylaxis is to be preferred to curative treatment. A man, aged 51 years, had cholecystgastrostomy performed for obstructive jaundice caused by cancer of the head of the pancreas following four days of preparation with glucose intravenously. Vitamin K and bile salts were given for one day only before operation, because the Quick prothrombin time and the Lee coagulation time had been reported as normal on two occasions. It was noted by the surgeon at operation that the liver was paris green in color and that no bile had been reaching the intestine. Immediately following operation, the prothrombin coagulation time rose from a normal level of 20 seconds to 30 seconds and then to 70 seconds; on the third postoperative day, signs of internal hemorrhage were apparent. By the time the latter report was received and before more vitamin K and bile salts could be administered, profuse bleeding occurred from the gastrointestinal tract. The concentration of hemoglobin fell to 4.9 gm. per 100 c.c. of blood and the patient lost consciousness. A single transfusion of 500 c.c. of blood had little effect on the prothrombin time as measured some six hours later. After 2 c.c. of an extract of vitamin K and 250 c.c. of bile had been administered by a duodenal tube on two successive days, the prothrombin time fell to a point within normal limits (20 seconds) and signs of active bleeding ceased. The same treatment in smaller dosage was continued daily thereafter and no further bleeding occurred.

The above experience has been duplicated in other instances and is by no means a special circumstance. Present difficulties are centered chiefly about

the detection of prospective "bleeders" and the delivery of vitamin K and bile into the intestinal tracts of patients who have active bleeding. Both are technical problems and, doubtless will be overcome; the important consideration is that in cases of both obstructive jaundice and parenchymatous hepatic injury the administration of bile and a vitamin-like material reduces the prothrombin time of blood to a point within normal limits and thereby controls or prevents active bleeding.

Summary

The principal requirements in the treatment of parenchymatous hepatic disease appear to be the maintenance of optimal conditions to allow for regeneration and repair of the parenchyma of the liver.

The use of special diets high in carbohydrate, vitamin concentrates, and liver extract parenterally are valuable in this connection. The treatment of hepatic insufficiency depends chiefly on the maintenance of a high intake of fluid with ample supplies of glucose; no specific protective substances, as yet, have been applied successfully to the treatment of this condition. The hemorrhagic diathesis associated with chronic hepatic disease and jaundice is dependent, in part, on deficient absorption of substances necessary for coagulation of the blood and, in particular, on depletion of the prothrombin of the blood because of hepatic injury. The use of bile, bile salts, and vitamin K in treating this condition has been discussed.

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CONGENITAL MALFORMATIONS OF THE PULMONIC AND AORTIC VALVES*

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Congenital malformations of the semilunar valves are relatively infrequent and usually consist of a variation in the number of cusps. Acquired malformations are seldom found, but must be carefully distinguished from the congenital form.

Simonds, in 1923, collected 209 records of cases of alteration in the number of cusps. In his paper on this subject, he reported his series together with those of three other investigators, a total of 43 cases discovered in the course of 15,666 postmortem examinations. Abbott, in 1932, in her tabulation of 1000 cases, reported 43 instances in which the defects were unaccompanied by other lesions and a total of 125 in which the anomaly was accompanied by other lesions. Simonds gave a logical explanation of the mechanism involved in the development of these defects.

Embryology

In the developmental division of the common arterial trunk into the aorta and pulmonary artery, two groups of swellings develop on the inner surface of the vessel. The four swellings distally situated with respect to the heart are the *anlagen* of the semilunar cusps; later, by descent and torsion of the vascular trunk, they come to occupy their normal position. The swellings proximally situated are two. Figures 1, 2, and 3, taken from Simonds' work, will suffice to show the normal division and the supposed manner of abnormal division of the arterial trunk.

Etiology and Types

A pulmonic valve consisting of four cusps is the most frequent malformation. In the majority of cases, there is no evidence of a previous inflammatory process and most likely this type of anomaly is the result of the occurrence of an extra pad or swelling in the common vascular trunk. From this explanation it would seem that four cusps would occur as frequently in the aortic valve as in the pulmonic valve. However, four cusps in the aortic valve are rare. The semilunar cusps are supposedly formed by a hollowing out process. It is probable that an abnormality in this mechanism would result in the formation of two cusps from one pad or swelling. This latter hypothesis does not seem plausible in view of the specimens examined in this series because all the accessory cusps appear as small, interpolated

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structures, well-formed, unattached to the adjacent cusps by adhesions, and approximately half the size of the normal cusps. If the deformity were the result of abnormal hollowing out, one would expect to find two small cusps which together would be equal in size to a single normal cusp.

The same possibilities apply to the anomalous aortic valve, consisting of four cusps. Why this type occurs so infrequently has not been explained satisfactorily.

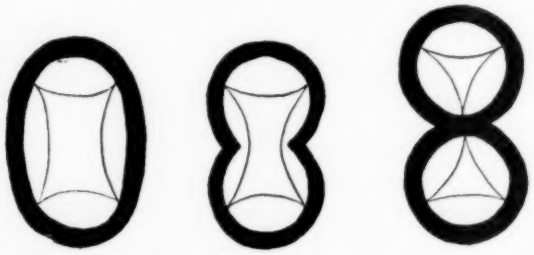

FIG. 1. Mechanism of normal division of common trunk into aorta and pulmonary artery with the formation of two sets of tricuspid valves (after Simonds).

FIG. 2. Abnormal division of the common trunk with resulting bicuspid aortic valve (after Simonds).

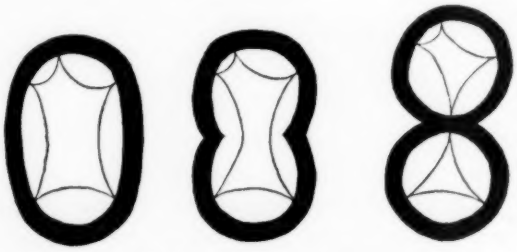

FIG. 3. Small interpolated cusp which may be the mechanism in the production of the four-cusp pulmonary valve (after Simonds).

The defects consisting of bicuspid pulmonary and aortic valves may be attributable more frequently to an inflammatory process than to a congenital defect of development such as those described. The bicuspid valve may have cusps of equal or unequal size. Bicuspid aortic valves are the more frequent. Prenatal processes or postnatal inflammatory processes possibly explain these defects. In the latter instance, the condition cannot be considered a congenital malformation. Postnatal deformity frequently is

caused by fusion of two adjacent cusps with a subsequent endocarditis, erosion, and ulceration of the partition, one cusp and one sinus of Valsalva remaining. In the case of a bicuspid aortic valve resulting from such inflammatory change, there is usually a ridge remaining in the middle of the larger cusp, which represents the point of cleavage. This aids in differentiating the congenital and acquired anomalies and has been employed by Bishop and Trubek in their valuable contribution to this subject.

In 1886, Osler, in describing the bicuspid aortic valve, advanced three characteristics of the congenital form which would serve to distinguish it from the acquired form. These are: 1. The free edge is usually straight, without nodular thickening, indicative of a corpus arantii. 2. The attached border presents a normal contour or a shallow groove, indicating the junction of two cusps. 3. The aortic side of the valve presents a more or less distinct raphé or frenum which divides or indicates a division into two sinuses. This raphé varies in position from that of an elevated ridge on the aortic wall to a single or double barred ridge extending a variable distance along the valve.

When marked calcification of the aortic ring and valves is found, the only definite proof of congenital malformation is lack of microscopic evidence of inflammatory change. Bishop and Trubek examined serial sections of the raphé which is present in the lower portion of the larger cusp. The presence or absence of other cardiac anomalies may also be of value in differentiating these conditions. Abbott expressed the opinion that the bicuspid aortic valve has an etiology that differs from that of a similar defect of the pulmonary valve.

Clinical Diagnosis

Deformities of the pulmonic and aortic cusps, unless associated with other cardiac anomalies, do not give rise to clinical signs or symptoms, and at present no criteria exist for the diagnosis of these defects.

Prognosis

If uncomplicated, these defects seem to cause no cardiac embarrassment. They are prone to undergo early calcification and are also subject to infectious processes such as subacute bacterial endocarditis. Thus, in spite of their benign clinical manifestation, they may cause death.

The material studied (table 1) fulfills the qualifications stated by Osler for the identification of congenital valvular defects; doubtful cases were not included, and sections were not examined microscopically.

In the 30 cases of alteration in the number of cusps of the pulmonic and aortic valves, the most common abnormality was the pulmonic valve of four cusps. This defect was found in 15 of the 30 cases. In the clinical records of the 15 cases, mention was not made of signs or symptoms that might have led one to suspect the presence of supernumerary valve leaflets. The

TABLE I
Summary of Material Studied

Lesion	Cases
Aortic valve	
2 cusps	9
4 cusps	3
Associated anomalies	5
Pulmonic valve	
2 cusps	3
4 cusps	15
Associated anomalies	2

defect as seen at necropsy consisted usually of a small, well defined cusp approximately half the size of a normal cusp. In two cases of the 15, two small cusps, equal in size, were found, and in both of these, the valves were competent. Four cardiac deaths were recorded, three of hypertensive cardiac disease and one of chronic adhesive pericarditis. Contrary to Foxe's observation, fenestrations were found in 5 of these 15 cases which involved all the cusps including the supernumerary one. In none of the 15 cases was there any associated congenital cardiac anomaly nor dilatation of the pulmonary artery.

Of the 30 cases, in 3 (10 per cent) there were bicuspid pulmonic cusps. One of the three patients concerned was a man who died of leukemia at the age of 23 years. At necropsy, the bicuspid pulmonic valve and dilatation of the pulmonary artery were discovered.

The second case of the three was that of a girl who died at the age of two months of cardiac insufficiency caused by stenosis of the pulmonary artery. There were no fenestrations in these cusps and no evidence of acute or chronic endocarditis. In the third case of the three, that of a boy 18 days of age, situs inversus with complete transposition was found at necropsy.

There were nine instances (33 per cent) of bicuspid aortic valve. Again in this group there were no clinical manifestations of valvular defect. Among these nine cases, however, there were five of coarctation of the aorta. The deformity seen at necropsy consisted of two valve leaflets, free at the margin in all cases but one; in that case vegetative endocarditis was present. These two valve leaflets were of approximately equal size and showed no evidence of previous inflammatory change which might confuse one in classifying the defect as acquired in nature. The case in which there was evidence of engrafted vegetative endocarditis had no features that would lead one to suspect previous inflammation. In two of these nine cases the coronary arteries came from behind one cusp and had separate openings. There were no fenestrations in these cusps. Two of the nine patients died of heart disease, one from hypertensive cardiac disease and one from vegetative endocarditis.

In three cases (10 per cent), the aortic valve had four cusps. These likewise were clinically silent defects. In all three specimens there was a

cusp only 0.5 cm. wide between the posterior and the right coronary cusp; this small cusp was well defined and was without evidence of previous inflammation. The margins of these cusps were remarkably free from change. There was one cardiac death and that was owing to coronary sclerosis. There were fenestrations in all the accessory cusps. In one case the remaining leaflets were involved while in the other two only the supernumerary cusp was fenestrated. Cardiac hypertrophy or dilatation of the aorta was not found.

Summary

Thirty examples of variation in the number of semilunar cusps are reported. In all cases, the lesions caused no clinical signs or symptoms. This statement, however, would be misleading if mention were not made that seven of these cases were associated with other cardiac anomalies of clinical significance and one of them, a bicuspid aortic valve, was the seat of fatal vegetative endocarditis. The four-cusp pulmonary valve was most frequently found and was associated relatively seldom with other anomalies. There was an equal number of bicuspid pulmonary valves and four-cusp aortic valves. Bicuspid pulmonary and aortic valves seem the most important because they are associated with grave cardiac anomalies. There was no case in which a defect was present in both valves.

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SOME OF THE RECENT BIOCHEMICAL CONCEPTS OF GASTRIC SECRETION AND THEIR APPLICATION TO CLINICAL MEDICINE *

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This paper is presented to summarize the data on gastric secretion which have originated from this department and which have been reported in a series of articles extending over several years. The investigation was undertaken with the idea of attempting to clarify some of the moot points in connection with the changes in the acid-base pattern of human gastric secretion; to learn, if possible, the secretory concentration of hydrochloric acid and of the neutral chlorides; to determine, if possible, the type of cell or cells secreting these neutral chlorides; and to study the inorganic phosphates during various phases of secretion. We were also interested in throwing more light on the nature of the substances which composed the protein and nonprotein nitrogen portion of gastric juice. These findings are given below and from them we have been able to propose a more satisfactory basis and method for titrating gastric secretion. We have also attempted to interpret the significance of these data in their clinical sense.

In order to better appreciate gastric secretion let us look upon the stomach as a membrane, a few millimeters in thickness, which forms the lining of the lumen in which the electrolytes and organic compounds of the blood are secreted or through which they are transferred. This membrane is composed of five main types of cell: (1) Chief body cells which secrete pepsinogen: (2) Parietal cells which secrete hydrochloric acid and perhaps neutral chlorides: (3) Mucus-neck cells which secrete mucus and salts; (4) and (5) The cylindrical epithelium of the foveola and enterochromaffine cells whose function in the formation of gastric juice is but poorly understood. Gastric juice is composed of the products of these cells and of the materials transferred from the blood and lymph to the surface of the stomach membrane. The secretory source from which come the proteins, nonprotein-nitrogen constituents and phosphates is not understood.

Our observations were made on the gastric juice of a group of 102 patients. The juice was aspirated before and at three consecutive half-hour periods after histamine stimulation.[1] The majority of these analyses were made on gastric juice which was not only free from swallowed saliva but also from bile; many of the specimens, being quite clear and limpid, were almost totally free of mucus. Mucus was removed by filtration through fine filter paper.

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Observations on Patients Secreting Hydrochloric Acid in Gastric Juice

The characteristic result of histamine stimulation on the secretion of gastric juice was a sudden increase in its volume. As the volume increased, the appearance of the fluid became clear and limpid. An elevation of the chloride and free hydrochloric acid concentrations accompanied this increased volume of secretion. There was always a concomitant decrease in the concentration of fixed base. This finding is illustrated in figure 1.

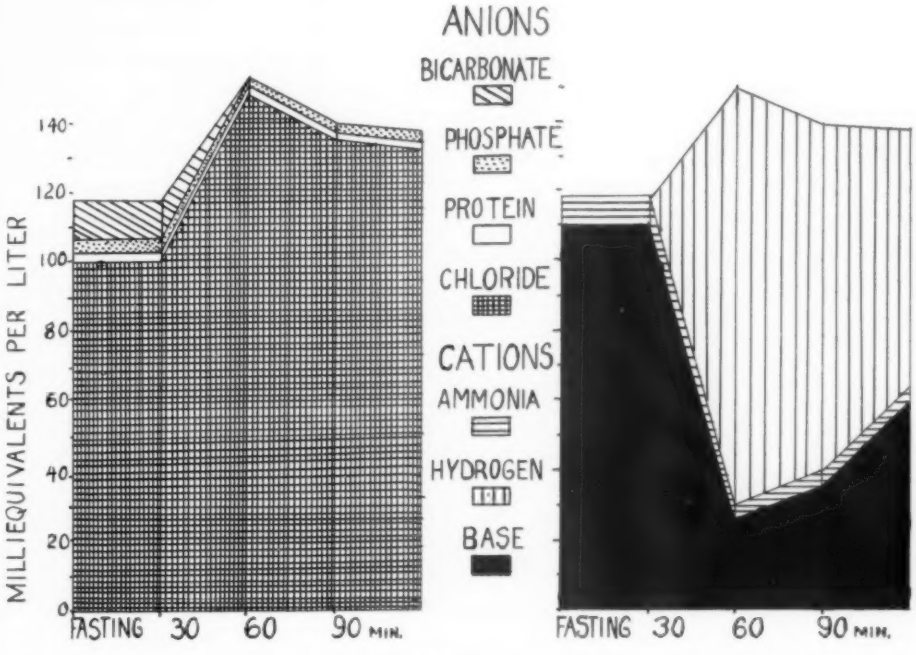

Fig. 1. Illustrating the changes in the acid-base pattern of gastric juice during successive phases of secretion before and after histamine stimulation.

When the total content of these substances was calculated from the concentration and the volume of secretion, it was shown that throughout the half-hour periods of observation the actual amounts of base secreted varied directly with the volume of secretion. The important factor in the increased volume of secretion was an increased production of hydrochloric acid. Consequently, during secretion of gastric juice the lowering of fixed base concentration represents dilution and not a decrease in the total volume secreted. As the stimulation of histamine waned there was a lowering in the concentration of total chloride and a more significant decrease in the hydrochloric acid content; to balance the latter change there was a corresponding increase in the concentration of fixed base. These findings were subsequently corroborated by Helmer.[2]

Our investigations have shown that the chloride concentration in the extracted filtered gastric juice in which hydrochloric acid is found varied from 80 to 160 milliequivalents, the latter figure approximating the total electrolytic strength of the blood serum. In the juice from the Pavlov pouches of dogs, the limits are reported to be higher, 130 to 165 milliequivalents.

Phosphates have been noted in the gastric secretion of animals and humans by various investigators, and our determinations showed that they were also present in the gastric juice of our patients. The amounts present varied from 2 to 8 milliequivalents in those who were able to secrete hydrochloric acid. During the height of the secretion of hydrochloric acid the concentration of phosphate diminished markedly and correspondingly with the base. The total amount secreted in half-hour periods remained about the same.

The diminution in the concentration of hydrochloric acid during the end stages of secretion has been noted by numerous writers. Some have followed Boldyreff [3] in believing this to be due to duodenal regurgitation: others,[4] who have found the same phenomenon to occur in the gastric juices obtained after stimulation from Pavlov pouches in the stomach of dogs, do not believe this theory. In our own studies we found the decrease in hydrochloric acid to occur even when the juice showed no change from its clear limpid appearance and no trypsin. We believe that, although the concentration of hydrochloric acid may be reduced by duodenal regurgitation, this is a secondary reaction, and that the primary cause is a decreased secretion in volume of acid with an increased secretion of neutral chlorides.

It is customary to speak of neutralization of hydrochloric acid by gastric mucus. In the unfiltered specimen this may serve to dilute the acidity but that it does not exert any important neutralizing effect may be seen in the following table which is typical of the findings noted in several patients.

Case 54:

Time Minutes	Description	pH	Volume c.c.	Milliequivalents per Liter		
				Free HCl	Total Chlorides as Cl	Base
Fasting	Mucus	1.7	1	78	125	47
30	Mucus +++	1.5	2	98	140	44
60	Mucus ++	1.4	2	121	158	40
90	Mucus	1.5	4	89	125	35

Observations on Patients not Secreting Hydrochloric Acid in the Gastric Juice

There were many patients in whom achlorhydria was noted but in whom no organic basis for this condition was demonstrated. We classified these

cases as benign achlorhydrias. In these cases it was questionable whether histamine caused any significant change in the volume of secretion. The chlorides fluctuated from specimen to specimen and in individuals. The lowest amount determined was 67 and the highest 118 milliequivalents per liter. The average was about 90 to 100 milliequivalents, i.e., approximately the same as for the chloride concentration in serum. In these patients the determination of bicarbonates was also important in that the amounts were significant; concentrations varying from 5.8 to 30.0 milliequivalents per liter were typical. The chloride and bicarbonate ions were balanced by fixed base and by ammonia, the former being the important ions and generally varying directly with the chloride, although somewhat higher, especially when the bicarbonates were elevated. The concentration of ammonia in these cases reached higher figures than in the acid-secreting patients and became a quantitatively important cation. The inorganic phosphates in the patients with achlorhydria varied from 2 to 16 milliequivalents. Half the determinations were above 8 milliequivalents per liter.

Discussion of Acid-Base Values

It is enlightening to consider the acid-base balance in the patients with benign achlorhydria before entering into a discussion of its behavior in the juices containing hydrochloric acid.

The juice we obtained from the achlorhydria patients was mucoid in character. After filtration it became clear and, as noted above, always contained chlorides and bicarbonates. After histamine stimulation there was usually some change in the acid-base pattern but not of a degree to produce any new departure. It seems likely that the chlorides found in cases of achlorhydria originate in the fluid accompanying the mucus secretion. This point is emphasized here, since it is possible that the parietal cells secrete chlorides as both acid and neutral salts and that the amount of each secreted depends upon the nature of the stimulus; consequently, these cells have to be looked upon as a possible source of secretion of neutral chlorides in achlorhydria.

A real difference was observed in the gastric secretion of these patients whose resting juice did not contain hydrochloric acid but who secreted it after histamine stimulation. The latter specimens showed a marked increase in the chloride concentration which was always associated with hydrochloric acid. If the chlorides found in the achlorhydric fasting juice represent in part neutral chlorides secreted by the parietal cells, it would be expected that there would be a decrease in the total amount of neutral chlorides secreted after histamine stimulation had caused an outpouring of hydrochloric acid. We have noted a decrease in concentration of neutral chlorides, but our calculations do not show a decrease in the total amount of chlorides secreted during the half-hour periods. Therefore, it is probable that the excess secretion of chlorides was caused solely by the stimulated secretion of hydrochloric acid.

From our graph (figure 2) it is evident that the total chlorides may be secreted in a concentration equal to the total electrolytic concentration of the blood serum, approximately 160 milliequivalents per liter. However, there are many more instances in which the total chloride concentration of the extracted specimens is hypotonic. This may be due to two causes: (a) The parietal cells may secrete chlorides at a concentration equal to or below the total electrolytic strength of the serum; or, (b) an isotonic parietal secretion of chlorides may be diluted by the lower chloride concentration of the fluid which accompanies the gastric mucus.

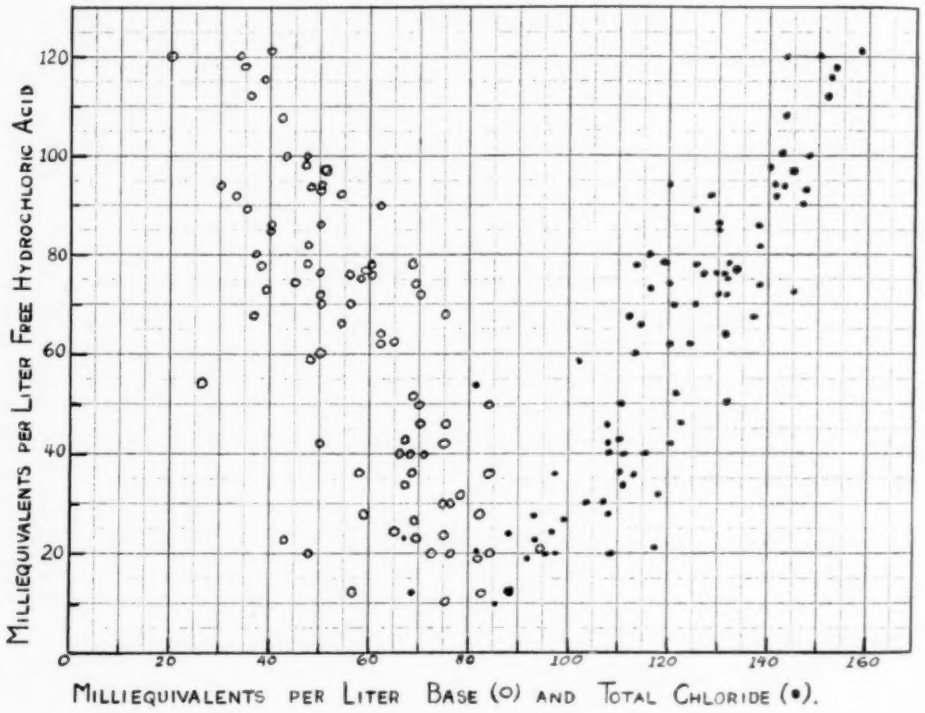

Fig. 2. Illustrating the amounts of fixed bases and of the total chlorides of gastric juice as a function of the hydrochloric acid secretion.

Although the chlorides of the extracted specimens were at times isotonic with the total electrolytes of the serum, hydrochloric acid was never so high; it did, however, approach this value. This may also be due to two causes: (a) The parietal cell may secrete chlorides as both hydrochloric acid and neutral chlorides. In analyzing the data obtained on our specimens this condition has to be taken into serious consideration; (b) an isotonic parietal secretion of hydrochloric acid may be diluted by the hypotonic chloride fluid which accompanies the gastric mucus.

Many of the gastric aspirations were clear and limpid and contained only minimal amounts of mucus. The combined neutral chloride and

acid chloride concentration of several of this type of secretion were hypotonic. Whether there was sufficient neutral salt in the fluid accompanying the mucus to dilute a postulated isotonic hydrochloric acid secretion we cannot say.

At this point it is enlightening to consider Hollander's investigations.[5] He obtained gastric secretion after histamine or food stimulation from Pavlov pouches made on the stomachs of dogs. From his findings he concluded that: "The parietal secretion is essentially an isotonic solution of hydrochloric acid, and contains no fixed base. The alkaline component is an isotonic solution the principal constituents of which are neutral chlorides and bicarbonates, the concentration of the former being appreciably greater than that of the latter. . . . Thus there can be no doubt that the chlorine content of the gastric juice of the highest degree of purity conceivable i.e. parietal secretion, is certainly in the form of the hydrochloric acid and not at all as alkaline or alkaline earth chlorides."

There can be little doubt from his words that he believes that the parietal cells secrete essentially only hydrochloric acid and at an isotonic concentration. He infers that the reason it is found in lower concentrations in the gastric juice is because it has been diluted by isotonic neutral salts or because it is neutralized, although only to a slight degree, by an isotonic solution of bicarbonates and that these latter substances are secreted by cells other than the parietal. If this conclusion is correct, it follows that at the onset of a free flow of "pure gastric juice" cells other than the parietal discontinue the secretion of chloride and bicarbonates. That this occurs in normal human gastric juice has not been proved.

At the risk of irksome reiteration it may be restated that, in the human gastric secretion, even the clearest specimens obtained were found to contain significant amounts of neutral chlorides. These it is true might represent that secreted with the mucus and it is very tempting to so credit their origin. If this were so, it would be reasonable to believe that hydrochloric acid was secreted into the human stomach in concentrations isotonic with the total blood electrolytes, as Hollander states is true in dogs. However, there is one reservation to the complete acceptance of this idea: hydrochloric acid is secreted into the stomach to provide a fluid of suitable hydrogen-ion concentration to permit pepsin activity. If "pure gastric juice" contained only hydrochloric acid, it would be of no value to the animal economy. Hollander says that the amount of organic material contained in his purest specimens was approximately zero.

We have found a fall in the protein nitrogen during the height of secretion, but significant amounts always persisted. We also made studies on the peptic activity of the specimens and found a direct relationship between the concentration of hydrochloric acid and the peptic activity. Perhaps in specimens of highest hydrochloric acid concentration more purified pepsin is to be found. The point to be made is that although hydrochloric acid of isotonic strength may possibly be secreted into the gastric juice the resultant

should not be called "pure gastric juice." A gastric juice without neutral chlorides may be a physiological and desirable one but so far it has not been demonstrated in man. A gastric secretion lacking in pepsin is neither physiological nor desirable.

Protein and Nonprotein Nitrogen Constituents

In addition to the studies described above observations were also made on other constituents, to be found in human gastric juice which was essentially uncontaminated with regurgitated duodenal contents and saliva. It was noted that, at pH 3.5, protein could be quantitatively precipitated by tungstates. After acidification of the mucus-free, limpid, filtered gastric juice with glacial acetic acid, a portion of the protein-like material could be precipitated by making the solution 33 per cent with acetone. This protein is crystallizable and has its isoelectric point at pH 3.5. We have called it gastro-globulin.[6] The amorphous material carried down with it all the pepsin and urease[7] in the original solution. Analyses of the crystals to determine their pepsin strength have not yet been made. Urease had been sought for as a means of explaining the relatively large amount of ammonia and the small amount of urea which were found in the original gastric juice.

It is important to note that the 33 per cent acetone filtrate contains a protein-like material to which is attached a carbohydrate molecule which forms osozones and which accounts for all the carbohydrates in the mucus-free gastric juice. That it represents the carbohydrate of dissolved mucus is unlikely, since the 33 per cent acetone-soluble material is dialysable and does not react chemically as mucus.

When the proteins and protein-like materials were removed from the gastric juice by tungstate at pH 3.5 the filtrates of a large series of cases were analysed for several nonprotein nitrogen constituents, namely: nonprotein nitrogen, urea, ammonia, uric acid and amino acid. It was found that in a series of patients secreting gastric juice of normal hydrochloric acid concentration the quantity of each was usually found within fairly restricted limits. Average amounts were: nonprotein nitrogen 25 to 35 mg. per cent; uric acid 2 to 5 mg. per cent; ammonia 5 to 7 mg. per cent; urea 2 to 4 mg. per cent; amino acids 5 to 7 mg. per cent. In benign achlorhydrias these constituents were present in about two-fold concentration; in pernicious anemia, in three-fold; in gastric carcinoma with achlorhydria, in four-fold. This last finding might be of diagnostic significance in the differential diagnosis of certain cases of gastric ulcer and carcinoma.[8] Specimens of the gastric juice of patients with nephritis and blood-nitrogen retention were found to have even higher amounts of the various nonprotein nitrogen constituents.

The foregoing data are of importance in understanding the significance of the conventional method of titration of gastric juice with NaOH when

Töpfer's solution and phenolphthalein are used as indicators. At the end point of Töpfer's, about pH 3.8, the free hydrochloric acid of the gastric juice is neutralized. However, at this point more than hydrochloric acid has been neutralized, for the iso-electric point of gastro-globulin is pH 3.5 and the other protein-like material is also precipitated at that point by tungstic acid. Consequently, it is fair to assume that in titrating the gastric juice to an end point with Töpfer's solution as an indicator, one not only determines the free hydrochloric acid but also the combined acidity. Therefore, titration from pH 3.8 to an end point with phenolphthalein, pH 8.5, determines the buffer value of the gastric juice to this point. This may be of significance, but as yet we have not found out its true meaning nor determined the value of such an observation in clinical pathology. If such titrations are still done they should be given their real terminology, namely, buffer value of gastric juice from pH 3.8 to 8.5, and the usage of the term "combined acidity" should be discarded.[9]

Discussion

The application of these more recent studies to routine clinical gastric analysis serves at least one useful purpose. It should limit the number of gastric analyses to those cases in which some definite information is desired. The information which we can gain from gastric analysis in general may be summarized as follows:

1. Presence or absence of hydrochloric acid.
2. Normal or excessive secretion of mucus.
3. Presence or absence of gross blood—not due to trauma.
4. Elevated non-protein nitrogen in certain cases.
5. Presence or absence of pepsin.

These five potentialities may be further discussed with some advantage.

1. Titratable acidity of the gastric juice varies markedly in the normal individual and also depends upon the method used for stimulating its flow. It may be considered as within normal limits if it is above 20 milliequivalents or units.

In peptic ulcer it is usually high and in carcinoma it is usually low. If one of these pathologic conditions is suspected, a high or low titratable acidity (including achlorhydria) is of significance. However, an achlorhydria is not always an indication of organic pathological change; Keefer and Bloomfield [10] have found that its incidence increases with age. A high titratable acidity is common in normal individuals.

In cases of macrocytic anemia, the proof of an achlorhydria is of fundamental import, but it must be remembered that the lowering of titratable acidity is to a large degree in direct relation to the decrease in the numbers of red blood cells and is, therefore, to be expected in association with the microcytic anemias.

2. In these days with so much attention being paid to the diagnosis of gastritis, an entity as yet not clearly understood, the demonstration of an increased secretion of gastric mucus may be of diagnostic importance.

3. Free blood in the gastric contents affords direct evidence of some pathological change and necessitates further and more detailed study of the wall of esophagus, stomach and duodenum.

4. An increase in the nonprotein nitrogen of the gastric secretion has been noted in several conditions. It is elevated in achlorhydria. It is especially high in the achlorhydria of cancer and may serve as a diagnostic aid in differentiating some cases of gastric cancer from peptic ulcer. It is noteworthy that it is markedly elevated in cases of nephritis in which there is blood-nitrogen retention. In these instances the stomach may be functioning as an organ of nitrogen excretion.

5. Pepsin has generally been reported as absent in cases of pernicious anemia, nor is it found in large infiltrating tumors of the stomach wall.

Conclusions and Summary

When gastric secretion stimulated by histamine begins, a fluid of changing acid-base equilibrium is secreted into the normal stomach. The element common to these changes is chlorine which is always found in the gastric juice. Appropriate stimulation will cause it to be secreted into the stomach in greater concentration than in the resting juice, and any significant increase in the chlorides is accompanied by an increase in the titratable acidity. It will often be accompanied by an increased volume of secretion of hydrochloric acid whose concentration in the extracted juice varies inversely with that of the fixed base (neutral salts). In human gastric secretion the absence of neutral salts has not been noted. Chloride concentration of the gastric juice equal to the total electrolytic strength of the serum has been found. In the majority of instances the former was below this level. The question of the monocellular source of the chloride secretion remains an open one.

The human gastric juice also contains a protein, gastro-globulin, which has been crystallized and is closely associated with pepsin and urease. There are one or more protein-like materials present and one or more of these have carbohydrate molecules attached. In this juice there are also such materials as ammonia, urea, uric acid and amino acid whose concentrations in the normal and certain abnormal individuals usually fall within predictable limits.

For reasons given above the usage of the term, *combined acidity*, is considered as incorrect and for clinical purposes the titration of gastric juice should be carried out to an end point with Töpfer's solution, approximately pH 3.8, since at this point practically all of the acid chlorides both as hydrochloric acid and protein chlorides have been determined.

It is believed that gastric analysis should not be resorted to as a routine diagnostic procedure but that it should be performed only in those cases in which information concerning this secretion is of real importance.

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SACCULAR ANEURYSM OF THE THORACIC AORTA: A CLINICAL STUDY OF 633 CASES *

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"There is no disease more conducive to clinical humility than aneurysm of the aorta."—Osler.

ANEURYSMS of various types have long been recognized. The first type to be described came to be known as *false aneurysm,* because following rupture or wounding of an artery, the sac which formed had for its walls the adjacent tissues or newly formed connective tissue. *Arterio-venous aneurysm* is the term applied to a communication between an artery and vein. If it is direct, the lesion is known as *aneurysmal varix,* whereas if there is an interposed sac it is named *varicose aneurysm.* Aneurysms may rarely be due to traction or erosion resulting from neighboring disease, and occasionally may be of mycotic, or of embolic origin.

True aneurysms are those in which one or more of the vessel coats form the wall of the tumor. The least common of this group is the *dissecting aneurysm* in which rupture of the intimal coat allows the blood to penetrate between the intima and media for varying distances, often with the formation of a new tube. The most frequent aortic aneurysm is the *dilatation aneurysm* in which usually only a portion of the vessel is dilated to a fusiform or cylindrical form, though occasionally the whole vessel and its branches may be dilated, and it is then known as a *circoid aneurysm.* Lastly there is the *saccular aneurysm,* a circumscribed bulging of the wall of a vessel with the formation of a sac connected to the lumen of the artery usually by a definite ring. It is the last disease entity with which this paper is concerned.

HISTORICAL

At the request of the Council of the Sydenham Society, John E. Erichson[1] translated and edited selections from the principal writers on the subject of aneurysm from the earliest times to the end of the eighteenth century. These were published under the title of "Observations on Aneurysms," in 1844. The quotations from the literature up to the nineteenth century, appearing below, have been taken either from this work or from Major's[2] "Classic Descriptions of Disease."

Galen,[1] in the second century, first described false aneurysms resulting from trauma to an artery. Four centuries later, Aetius,[1] in a similar description, also included lesions due to rupture of an artery without external injury, especially as seen in the neck, saying, ". . . it very commonly happens to women during parturition, on account of the forcible detention of spirits."

Fernel,[1] 1542, in a discussion of aneurysm first called attention to those of internal arteries. He wrote, "It also sometimes occurs in the internal arteries, espe-

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cially in the chest, or about the spleen and mesentery, where violent throbbing is frequently observable."

Late in the sixteenth century, Ambroise Paré [2] wrote the first published note of the relationship of aneurysm to syphilis. He said "The Aneurismes which happen in the internal parts are incurable. Such as frequently happen to those who have often had the unction and sweat for the cure of French disease, because the blood being so attentuated and heated therewith that it cannot be contained in the receptacles of the Artery, it distends it to that largeness as to hold a man's Fist; Which I have observed in the dead body of a certain Taylor who by an *Aneurisma* of the Arterious vein suddenly whilst he was playing at Tennis fell dead, the vessel having broken; his body being opened I found a great quantity of blood powred forth into the capacity of the Chest, but the body of the Artery was dilated to that largeness I formerly mentioned; and the inner coat thereof was bony."

Richard Wiseman,[2] in his works published in 1696, gave two causes for internal aneurysms. "1. The internal Cause is, the impetuousity of the Bloud, which moving with greater violence in its Chanels than the Artery can sustain, doth force its way through the side of the Vessel. . . . Secondly, from the quality of the Bloud, which being too sharp or thin, erodes the Vessel; or, being highly fermented by other causes, bursts through all."

Lancisi,[1] 1728, published an extensive discussion of aneurysm. He applied the terms "true" and "false" but not in the modern sense. True aneurysms were those in which a weak arterial wall occurred either from external trauma or from internal causes as "deficiency or debility of the villi." False aneurysms were those due to "increased power of the impulse, . . . produced by violent efforts in porters and trumpeters." In his Proposition XXXII "On the mode of formation, the causes, and symptoms of a syphilitic aneurysm" Lancisi described skeletal erosion by an aneurysmal sac. "As an acrid fluid, distilling from the aneurysmal cyst or sac, may penetrate as far as the bones or ligaments, which it may gradually corrode, and wear away; so, on the contrary, it may sometimes happen that the lymph, abounding in syphilitic humours, may, first of all, give rise to congestion in the bones and ligaments; but by and by, having become more acrid, and settling in the external coat of the artery, it may begin to corrode, and thus to dilate it into an aneurysm." He also discussed mercury as a cause of aneurysm: "The whole influence of mercury in giving rise to aneurysms consists in the strength of the impulse by which the weakened lymph and blood are forced and tossed about on all sides." Further, he believed that "mercurial fluid" in the vessels caused distention of them just as it caused swelling of the salivary glands. Lancisi also described the clot which often forms in aneurysmal sacs, as follows, "The polypous body, by obstructing entirely the canal of the vessel prevents the direct passage of the blood, interrupting the circulation, and compelling the fluid to take a collateral route. Hence from this cause, the pulse is often obliterated at the wrist, as happened to the Marchioness Paulutio."

In 1736, Petit [1] described aneurysms due to puncture of a vessel as *aneurysms of effusion,* and others as *aneurysms by dilatation.* He pointed out that the latter presented a thrill, rarely present in the former, and that by applying the ear, a distinctive sound could be heard.

William Hunter,[1] in 1757, published a detailed account of the case of a patient with an aneurysmal sac pointing through the chest wall, which oozed blood for some weeks before death. An autopsy was done. In his discussion he used the terms "true" and "false" in the modern sense. Also he described the symptoms of pressure he had encountered in five cases of aneurysm.

Donald Monro,[1] 1760, in a long paper on the subject of aneurysm, made the first reference, in the English literature, to syphilis. He said, "Sometimes a scorbutic or venereal taint, or some other acrimony in the blood, has been accused."

In 1761, Morgagni [2] published "The Seats and Causes of Disease." In 1725 he had had the opportunity to perform an autopsy on the body of a young woman who had died during sexual intercourse. A small aneurysm was found, one-half inch above the aortic valves, which had ruptured into the pericardium. The first description of the gross pathology of syphilitic aortic disease is as follows: "That is to say, in some places whitish marks of a future ossification occurred; in others, some small foramina, as it were, had begun to be formed; and in still other places were paralleled furrows, drawn longitudinally; and in this manner was the surface of the artery unequal here and there." Even earlier, in 1708, Morgagni had noted similar changes in the aorta of another young woman who had died due to aneurysmal rupture.

Corvisart [3] described, in 1806, various symptoms and signs which may be encountered in aortic aneurysm, pointing out that the diagnosis is difficult unless the sac points externally. He called attention to the thrill, retro-manubrial dullness on percussion, smallness and inequality of the pulse, and a whistling sound when the sac compresses the trachea. Bertin [4] in 1833, and Flint [5] in 1859 added further to the clinical description of aneurysms of the thoracic aorta. In 1878, Oliver [6] published a short note describing tracheal tug.

Welch,[7] in 1875, presented data attempting to prove that syphilis was the cause of aortic aneurysm in 66 per cent of 53 cases of aneurysm found at autopsy in soldiers. He described his gross findings, and stated, "this disease of the aortic coats may retrogress . . . but if extensive or severe, as a rule it is followed by one of three fatal phases—formation of aneurysms, implication of aortic valve, or hypertrophy with or without dilatation of one or more of the heart's cavities." The paper was very unfavorably received and its discussants, among whom was Sir William Gull, openly expressed their unbelief. An unfriendly review soon followed in the *Lancet*. Welch answered this by a published letter in the same journal.

In 1888, Thoma [8] wrote concerning the pathology of aneurysmal formation, and considered as its cause, arteriosclerosis due to marasmus, lead, syphilis, gout, et cetera.

It had been recognized for some time that syphilis was mainly a vascular disease, when Döhle [9] in 1895 discussed the microscopic changes in syphilitic aortitis and their bearing upon the formation of aneurysm. In this paper he reviewed a case which he had reported in 1885, describing the pathology of syphilitic aortitis.

Then came the discovery of the *Spirocheta pallida* by Schaudinn and Hoffmann [10] in 1905, in the primary lesions of syphilis. In the following year, Reuter [11] described the organism in the wall of the aorta in aortitis.

The importance of syphilis as a cause of aneurysm thus became established.

Material

Studies of large series of cases collected from the literature have appeared in the past, but such material drawn from many sources suffers from lack of uniformity in study. Hare and Holder [12] and Boyd [13] have published the largest collected reports.

From 1905 to 1935 inclusive, 1038 patients were admitted to the wards of Charity Hospital, in New Orleans, in whom a diagnosis of aneurysm of the thoracic aorta was made. At the Vanderbilt University Hospital, from 1925 to 1936 inclusive, 75 patients were so diagnosed in the wards and clinics. The combined material from the two institutions (1113 patients) represents a recorded experience with this disease of such magnitude as to justify analysis, since it constitutes the largest material subjected to review.

From the 1113 hospital records of aneurysm of the thoracic aorta, there have been selected 633 for this study. The remainder were excluded because they did not meet the rigid criteria demanded for inclusion. These criteria were as follows:

1. The demonstration of aneurysm at necropsy (165 cases).
2. A history and physical findings compatible with the presence of aneurysm, and in addition either, (*a*) a visible expansile tumor eroding the chest wall (120 cases) or, (*b*) the roentgenologic evidence of a saccular aneurysm arising from the aorta.

On the basis of such rigid selection, it seems that any error is on the side of failure to include in the study some cases which were discarded.

Incidence

The aorta is the most frequent vessel to be involved in the formation of aneurysm. Further, it is the thoracic portion which is especially affected. The frequency of aneurysm in the thoracic aorta as compared with other vessels is shown in table 1. (Aneurysms due to trauma are not included.) Seventy-three of the cases of aneurysm of the abdominal aorta were studied and reported by the author.[14]

Table I

Diagnosis of Aneurysm in the Charity Hospital Group (1905 to 1935)

Site of Aneurysm	Number
Thoracic aorta	1038
Abdominal aorta	95
Carotid artery	12
Innominate artery	10
Subclavian artery	3
Iliac artery	2
Pulmonary artery	2
Anterior vertebral artery	1

The incidence of aortic aneurysm fluctuates within wide limits in various countries, and in the United States it varies with the section of the country, because of the unequal distribution of the negro race. Obviously the incidence will differ as between private and charitable institutions.

There are surprisingly few publications dealing with the incidence of aortic aneurysm in large series. Those available have been considered from two viewpoints, the clinical and the necropsy incidence.

The clinical incidence will vary a great deal with the accuracy of the study. Generally patients studied on hospital wards will show a greater number of aortic aneurysms than patients in the Out-Patient services. Boyd [13] says aneurysm is 15 times more common in hospital series than in ambulant series, but gives no data as proof of this. In table 2 have been assembled the statistics of the clinical diagnoses of aortic aneurysm in

TABLE II

Frequency of the Clinical Diagnosis of Aortic Aneurysm in Various Hospitals

Author	Hospital and Years	Number of Aneurysms	Ratio per Patient
Browne [16]	St. Bartholomew's Hospital, 1867–83	228	1 : 350
Eichors [16]	Zürich Medical Clinic, 1884–1901	28	1 : 1200
Wolpert [16]	University of Berlin, O. P. D., 1895–1905	55	1 : 1359
Dahlen [15]	Stockholm (Hospital), 1897–1906	22	1 : 790
Osler [17]	Johns Hopkins Hospital (Medical Wards), 1889–1909	231	1 : 105
Allen [17]	Melbourne Hospital	298	1 : 157
Lemann [18]	Touro Infirmary, O. P. D.	47	1 : 300
Kampmeier	Vanderbilt University Hospital, O. P. D. and wards, 1925–1936	75	1 : 1080
Kampmeier	Charity Hospital, wards only, 1905–1935	1038	1 : 756

various hospitals throughout the world. They are not comparable because some are from ward studies and some from out-patient series. Further, the statistics probably include aneurysms of various types, whereas the present study deals only with the saccular variety. At Vanderbilt University Hospital the diagnosis was made 75 times giving an incidence of about 1 : 1080. However, if this is corrected by applying the criteria of the present study only 44 cases of the 75 are found acceptable; the incidence then becomes 1 : 1840. In the 30 year period covered by the Charity Hospital series, there were 774,774 admissions, and since the diagnosis of aortic aneurysm was made 1038 times, the incidence was 1 : 756. But if only the 593 acceptable cases are taken, the ratio is 1 : 1306 admissions.

In table 3 are given the results of various necropsy studies. Lucke and Rea [16] have collected the material from Germany, Austria, the Scandinavian

TABLE III

Incidence of Aortic Aneurysm at Necropsy in Various Countries and in Certain Hospitals in the United States

	Hospital	Necropsies	Ratio
India	Calcutta Medical College [17]	5,900	1 : 196
Germany and Austria [16]		160,145	1 : 111
Scandinavian countries [16]		5,490	1 : 109
Great Britain [16]		36,500	1 : 74
United States		16,200	1 : 41
Lucke and Rea [16]	Philadelphia General Hospital, 1867–1916	12,000	1 : 43
	University of Penn. Hospital, 1875–1916		
Osler [19]	Johns Hopkins Hospital (Med. Wards)	2,200	1 : 34
Warthin [20]	University of Michigan Hospital, 1909–1929	1,675	1 : 52
Kampmeier	Vanderbilt University Hospital, 1925–1936	1,653	1 : 331
Kampmeier	Charity Hospital, 1905–1935	12,053	1 : 73
Author's Negro male	Med. Service, Charity Hospital (4 years)	284	1 : 18

countries, Great Britain, and from the United States. Unfortunately the statistics for this country are probably not representative, because of the total of 16,200 necropsies, 14,400 occurred in Philadelphia Hospitals and in Johns Hopkins Hospital which probably admitted more colored patients than comparable northern hospitals. Boyd[13] states that postmortem statistics indicate that aneurysms account for 0.1 to 0.9 per cent of deaths in American cities. In the present study, it was found that at Vanderbilt University Hospital, where relatively few negroes are admitted, the incidence was one saccular aortic aneurysm to 410 necropsies. At Charity Hospital 12,053 necropsies had been performed in the 30 year period, with an incidence of one case of thoracic aneurysm to 73 necropsies. In order to contrast the incidence of postmortem proved aortic aneurysms in negro males alone with that of the general hospital frequency the following figures are of interest. In a four year period 284 necropsies were done on patients from the 29 bed, negro male division of the medical service under my care at Charity Hospital. Among these were 15 cases of saccular aortic aneurysm, giving an incidence of 1 : 18 necropsies.

TABLE IV

Incidence of Aortic Aneurysm in 5 year Periods as Related to Hospital Admissions

Years	Accepted Cases of Aneurysms	Hospital Admissions	Ratio of Aneurysms to Admissions
1906–1910 inclusive	42	47,736	1 : 1136
1911–1915 inclusive	79	74,117	1 : 925
1916–1920 inclusive	91	90,613	1 : 995
1921–1925 inclusive	109	105,330	1 : 966
1926–1930 inclusive	136	166,086	1 : 1221
1931–1935 inclusive	134	282,480	1 : 2854

Table 4 is of interest because it may indicate the trend of the occurrence of aneurysm. The incidence of aneurysms is analyzed with reference to admissions. In the single years as well as for the 30 year period, the cases accepted for this study were roughly about one-half of the cases diagnosed. Thus this table presents no special selection. This decrease, by more than half, in the frequency of aneurysm lends support to the belief that the lesion is becoming more infrequent, whether due to more frequent and adequate treatment, or to some other cause.

ETIOLOGY

Syphilis. This disease is accepted as the specific etiologic factor in the great majority of cases of aneurysm of the larger vessels.

Though it is recognized that the history of a genital sore does not necessarily mean that the sore was syphilitic in nature, such presumptive evidence will, nevertheless, be presented. A history of a genital chancre was obtained

from 241 patients (38 per cent) and of a labial lesion in one instance. Only five of the 242 patients were women, and each of these five gave a history of a vulval lesion.

The date of the primary sore is no doubt inaccurate in many of the patients, especially among the negroes, but in table 5 are given the data as

TABLE V

Time Elapsed from Chancre to Onset of Symptoms

Years not specified	22	
1–5 years	21	
6–10 years	30	
11–15 years	45	
16–20 years	68	(one lip)
21–25 years	24	
26–30 years or over	32	
Total	242	

recorded regarding elapsed time from the sore to the date of history taking. The intervals ranged from 5 to 30 years. Noteworthy is the fact that the second decade (11 to 20 years) before admission included 113, or about one-half, of the aneurysm patients reporting a genital lesion. It thus appears probable that aortic aneurysms make themselves evident from 10 to 20 years after infection in untreated individuals. Among the 4000 cases collected from the literature by Boyd,[13] 200 gave a history of a primary lesion, and an average of 20 years had elapsed from the time of infection to the date of diagnosis of aneurysm.

The blood Wassermann test presents more acceptable evidence of syphilis than a history of a genital lesion. This test was done in 467 patients or 73.7 per cent of the material. (In the remainder the test was not done, either because the patients were seen in the first decade covered by this study, or because early death after entering the hospital prevented it.)

Of the 633 cases, 467 had a Wassermann test, 112 had neither a serological test nor a history of a genital lesion, and 54 had had a primary lesion but no Wassermann test. Of the 467 tested cases, 291, or 62 per cent, gave a positive Wassermann reaction, and 176, or 38 per cent were negative. Among the 291 positive reactors were 118 (40.5 per cent) with a history of a genital lesion. Among the negative reactors were 70 (39 per cent) who had had a sore.

As evidence of syphilis, then, there was a positive Wassermann test or a history of a genital sore (with or without a negative Wassermann reaction) in a total of 415 cases. In addition there were two cases without either of these criteria, but with a positive spinal fluid. Thus there was clinical evidence of syphilis in 417 cases, or in 65 per cent. Necropsy was done in 35 cases in which the Wassermann test was negative, and in 73 cases without serological study. In these 108 examinations the gross or microscopic diagnosis of syphilis was made 33 times (three of these had

had a chancre). It is thus found that 447, or 70 per cent, of the cases in this study may be accepted as being definitely syphilitic. The necropsy protocols of the early years of the period covered, and of the coroner cases were brief and confined to gross findings, thus accounting for the few cases presenting pathological evidence of syphilis in the absence of clinical studies. It seems quite obvious that if satisfactory examinations had been carried out in the early cases that had neither Wassermann tests nor careful postmortem studies, the proof of syphilis would have been much more frequent.

To obtain more accurate information in this respect, the Vanderbilt cases, and the cases of the last decade of the Charity Hospital were separately analyzed. Among the 44 Vanderbilt Cases were 16 with either a negative or no serological test. Nine of the 16 had either a history of a sore, positive necropsy diagnosis, or aortic insufficiency as evidence of syphilis. These in addition to those with positive Wassermann tests give an incidence of proved syphilis in 84 per cent. Of the 269 cases of saccular aneurysm, occurring in the last 10 years of the Charity Hospital study, 117 had either a negative or no Wassermann test. Of these 36 had a history of genital sore, 17 more had a necropsy diagnosis of syphilis, and 12 had aortic insufficiency. These cases in addition to the 152 with a positive serological reaction give an incidence of syphilis in 81 per cent.

Arteriosclerosis. Arteriosclerosis is occasionally thought of as a cause of aneurysm. That atheroma may be a secondary factor in conjunction with syphilis seems probable, but the location of the process in the mesaorta which results in a bulging of the aortic wall, with its predominant intimal involvement, indicates that arteriosclerosis is not a major etiologic factor. Old age itself does not offer proof that arteriosclerosis is the cause of aneurysm. In this series, there were 19 patients over 50 years of age, in whom necropsy showed syphilitic lesions. Three of these were over 70 years old.

Hypertension. This condition has in the past been assigned a rôle in the production of aortic aneurysm. As in the case of arteriosclerosis, if hypertension plays any part at all, it must be only secondary in nature, since it does not lead to mesaortitis. Possibly hypertension in the presence of disease of the media may aggravate the tendency to saccular dilatation. It is important to emphasize in this connection that only hypertension, which is unassociated with aortic insufficiency, might be of significance. In table 6 are analyzed 64 cases of aneurysm with a systolic blood pressure of over 160 mm.

No cases of aneurysmal sac on a mycotic or embolic basis were found, nor were there any due to tuberculosis.

Race. Aneurysm appeared most often in the negro. This is not surprising because of the greater incidence of syphilis in this race and because treatment is so commonly neglected. Of the 633 cases, 482, or 76 per cent,

TABLE VI

Sixty-Six Cases of Aneurysm with a Systolic Pressure of Over 160 mm.

Age	Wass. Pos.		Wass. Neg.		No Wass.		Syphilis Autopsy	Atheroma Autopsy	No Data Autopsy
	Cases	Aortic Insuf.	Cases	Aortic Insuf.	Cases	Aortic Insuf.			
26–35 yrs.....	2	—	1	—	—	—	—	—	—
36–45 yrs.....	11	5	5	4	2	1	1	—	1
46–55 yrs.....	12	3	10	3	1	—	4	—	2
56–65 yrs.....	9	3	6	1	—	—	—	—	—
66–75 yrs.....	4	1	2	—	—	—	—	1	—

were negroes, and 24 per cent, or 151 were white. (This series included one Filipino and one Puerto Rican.)

In the Vanderbilt University Hospital group the incidence of white to colored patients with aneurysm was 1 : 5.3. In the Charity Hospital group it was 1 : 3.1, whereas the ratio of white to colored hospital admissions was 1.2 : 1 in the last decade. Osler's [19] Johns Hopkins Hospital series showed a ratio of white to negro patients with aneurysm of 2.6 : 1, but with an admission ratio of 4 : 1. Lucke and Rea,[16] in Philadelphia, found a ratio of white to colored patients of 2.3 : 1 while admissions were 15 : 1.

Sex. Since syphilis is the accepted etiologic factor in production of aneurysms of the large vessels, and because syphilis is found more often in the male, aneurysm of the aorta would be expected to develop more often in this sex. This is shown to be true in the present series. Thus, 379 (59.8 per cent) were negro males, 131 (20.8 per cent) were white males, 103 (16.1 per cent) were negro females, and only 18 (2.8 per cent) were white females. To express it in another way, the incidence of thoracic aortic aneurysm was in the ratio of, male to female, as 3.7 : 1 in the colored, and as 7.9 : 1 in the white group. If these figures are averaged, the ratio is 5.8 : 1. Boyd [13] in his 4000 collected cases found a ratio of 5.8 males to 1 female, and Lucke and Rea [16] in necropsy statistics, found it to be 4.2 : 1.

Age. Generally, the members of the medical profession think of aortic aneurysm as occurring in patients of about 40 to 50 years of age. Age in itself is a minor factor, however. Only the years elapsed since the primary syphilitic infection are of importance.

Therefore, in the case of the negro, whose sex-life often begins early, and whose syphilitic infection is more often acquired earlier, it is not uncommon to see full-blown cardiovascular syphilis at a comparatively early age. In this series, nine gave an age of from 20 to 25 years; seven negroes and one white were males, and one was a negress. In the 26 to 35 year old group, there were 62 males and 18 females of the colored race, and 8 males and 3 females of the white race. Sixteen per cent of all the cases were in persons of less than 35 years of age.

The highest incidence of aortic aneurysm in the negroes was in the 36 to 45 year old group, where there were 130 males, and 42 females, or 32.3 and 40.7 per cent of their respective groups. The greatest incidence among white males was in the 46 to 55 year group, with 46 cases, or 34.5 per cent. Among white females six cases, 33 per cent, appeared in each 10 year span of 46 to 55, and 56 to 65 years. Table 7 presents the distribution of aortic aneurysms with regard to age, sex, and race.

Occupation. (Table 8.) Hard manual labor has been accepted as being of great secondary importance to syphilis in the causation of aortic aneurysm.

TABLE VII

Distribution of 633 Aortic Aneurysms, as Regards Age, Sex and Race

Age in years	Other Races	Negro Males	White Males	Negro Females	White Females
20–25 yrs. inclus.	—	7	1	1	—
26–35 yrs. inclus.	—	62	8	18	3
36–45 yrs. inclus.	1	130	31	42	1
46–55 yrs. inclus.	—	115	46	29	6
56–65 yrs. inclus.	1	45	31	12	6
66–75 yrs. inclus.	—	18	13	1	1
76–85 yrs. inclus.	—	2	—	—	1
Age not given	—	—	1	—	—
Total	2	379	131	103	18

TABLE VIII

Occupation of 633 Patients with Aortic Aneurysm

	Negro	White
Males		
Laborer	280	49
Farmer	25	10
Skilled laborer	4	11
Clerk	1	9
Baker	—	4
Barber	1	1
Watchman	1	1
Cook or waiter	9	2
Peddler	2	1
Railroadman	—	6
Merchants	—	3
Chauffeur	3	—
Minister	2	—
Porter	8	—
Miscellaneous	6	4
No occupation given	37	30
	379	131
Females		
Housework	65	6
Housewife	5	10
Laundress	9	—
Cook	9	—
No occupation	15	2
	103	18

This led Osler to join 'Venus, Mars and Vulcan' as a triad responsible for aneurysm. The rôle of heavy work is borne out in the present study. The table indicates the large percentage of males who engaged in hard work as common labor or in farming.

As was pointed out above, the incidence of aneurysm in females is one to about six in males, whereas the incidence of syphilis in the two sexes is usually given as four females to six males. The difference in these ratios is probably due to less exposure and lighter work in the female, though it must be recognized that generally syphilis runs a more benign course in the female.

Anatomical Classification

From an anatomical viewpoint, aneurysms may be classified according to the portion of the intra-thoracic aorta involved. This anatomical classification is of clinical value from the standpoint of the symptomatology, physical signs, prognosis, and complications which may be expected.

This paper will consider the clinical aspects of aneurysmal sacs arising from the four main portions of the thoracic aorta—ascending, transverse, and descending segments of the arch, and the descending thoracic aorta. In the study of the 633 cases, two additional classifications were added. In one group the site of the sac could not be accurately placed, and therefore these 14 cases were labelled merely as 'aneurysms of the arch.' The second group consisted of 23 cases in which there were two or more sacs which obviously might lead to mixed clinical pictures.

The detailed study of this paper is therefore based upon 596 cases distributed among the four anatomical divisions of the thoracic aorta. See table 9 for the distribution as related to sex and color.

Table IX

Anatomical Site of Sac as Related to Sex and Color

Aortic Segment	Negro Males	White Males	Negro Females	White Females	Other Races
Arch	6	6	1	1	—
Ascending arch	129	39	40	6	—
Transverse arch	124	34	40	5	2
Descending arch	85	40	18	4	—
Thoracic aorta	22	5	3	—	—
Multiple sacs	15	7	1	2	—

For years saccular aneurysm arising from the ascending arch has been known as "aneurysm of signs." Sacs arising from the aortic arch, between the aortic valve and origin of the innominate artery, may attain great size, often with few symptoms, and tend to point anteriorly through the chest wall. There were 214 examples of this type. For the sake of simplicity,

four cases in which the sac arose from the sinuses of Valsalva have been included in this group.

Transverse arch aneurysm is known as "aneurysm of symptoms." Saccular aneurysm was found at this site in 205 cases. This segment of the arch is intimately related to the esophagus, trachea, left bronchus and left recurrent laryngeal nerve. Because of narrowness of the thoracic inlet and the presence of these vital structures, it is obvious that aneurysms of the transverse arch are prone to produce symptoms since, as they expand, they encroach upon these structures.

The descending arch lies to the left of the third to sixth dorsal vertebrae, close to the esophagus and left bronchus. Often a sac in this area is silent, but when it points, it does so posteriorly through the chest wall to the left of the spine. There were 147 cases of aneurysm of this segment.

Much less common than any of the above groups are aneurysm of the descending thoracic aorta, that part of the aorta extending from the sixth to twelfth dorsal vertebrae. Sacs arising from this portion often reach immense size without symptoms or signs, and it is in this group that the clinician is most likely to be surprised upon roentgen-ray or postmortem examination. There were 30 cases of aneurysm in this division of the aorta. In his 4000 collected cases, Boyd [13] found the ratio of sacs in these segments to be, in order, 10–7–3–1; in the present study the ratio is 7–7–5–1.

Chief Complaint

In table 10 are listed, with their frequency, the complaints which brought the patients to the hospital. These will be more fully considered under a discussion of symptomatology.

Table X

Chief Complaint

	Ascend. Arch (214 cases)	Trans. Arch (205 cases)	Descend. Arch (147 cases)	Descend. Thor. (30 cases)
Pain	112	114	103	25
Dyspnea	94	80	42	3
Cough	35	45	34	3
Tumor	37	28	10	2
Palpitation	18	13	8	3
Hoarseness	10	19	20	—
Dysphagia	5	13	5	—
Hemoptysis	2	3	6	1
No history	9	7	8	1

Most important is the fact that pain was the main symptom the patients complained of. This is significant if the figures are compared with those of the table of symptoms, where dyspnea is found more frequently than pain, though it appears less often as a complaint.

Symptomatology

The duration of symptoms in the majority of cases had been from two to 12 months. In table 11 the cases are grouped according to the duration

Table XI

Duration of Symptoms

	Ascend. Arch (214 cases)	Trans. Arch (205 cases)	Descend. Arch (147 cases)	Descend. Thor. (30 cases)
1 wk. or less	23	7	2	1
1 to 4 wks.	26	31	18	5
1 to 3 mos.	40	38	26	3
3 to 6 mos.	36	41	28	8
6 to 9 mos.	15	16	11	2
9 to 12 mos.	32	23	18	4
12 to 18 mos.	9	10	7	2
18 to 24 mos.	14	12	10	1
2 to 3 yrs.	8	7	7	3
4 yrs.	2	1	—	—
5 yrs.	2	5	—	—
6 yrs.	4	—	3	—
10 to 15 yrs.	1	2	—	—
Yrs. ?	2	—	2	—

of symptoms, whenever this was recorded. The time elapsed from the onset was no more than one year in 71 per cent of the ascending, 76 per cent of the transverse, 70 per cent of the descending, and 76 per cent of the descending thoracic segment cases. In a few instances in each group, symptoms had been of less than a week's duration, and in an occasional instance as long as from 5 to 15 years.

In table 12 are given the symptoms, and frequency of these, in saccular aneurysms of the thoracic aorta.

Table XII

Symptoms of Aneurysm of the Thoracic Aorta

Symptoms	Ascend. Arch (214 cases)	Trans. Arch (205 cases)	Descend. Arch (147 cases)	Descend. Thor. (30 cases)
Pain	132	123	106	26
Dyspnea	140	131	76	10
Cough	117	119	75	9
Palpitation	32	18	11	3
Hoarseness	34	63	36	2
Dysphagia	16	40	12	2
Hemoptysis	18	17	19	3
Tumor	37	32	10	2
Edema of legs	43	24	14	1
"Choking spells"	2	15	2	—
Vertigo	17	20	7	—
Sputum	42	45	26	5
No history	9	7	8	1

Pain was present in about 60 per cent of the cases of ascending and transverse arch groups. It occurred in 72 per cent of the descending arch and in 86 per cent of the descending thoracic aneurysms. Usually the pain was described as pressing, boring, and, more often than not, constant in nature. Undoubtedly in most instances such pain can be explained by pressure of the sac either upon certain structures, or, more often, on portions of the chest wall giving pain of segmental distribution. In some cases the pain was described as of anginal type, probably due to either involvement of the coronary orifices in the syphilitic aortitis, or to aortic insufficiency, either of which would lead to myocardial ischemia.

The site and radiation of pain is of importance because of the erroneous diagnoses which often result, and therefore these features have been tabulated in table 13. In a fair number the detailed site of pain was not given,

TABLE XIII

Site and Radiation of Pain in Aortic Aneurysm

Site of Pain	Ascend. Arch (214 cases)	Trans. Arch (205 cases)	Descend. Arch (147 cases)	Descend. Thor. (30 cases)
Chest, in general	35	37	16	—
Chest, right	31	3	4	—
Chest, left	2	20	25	6
Chest, precordial	11	8	4	—
Chest, retrosternal	5	9	4	—
Chest, substernal	2	6	—	1
Neck	17	6	4	—
Face or head	2	2	4	—
Shoulder, right	13	7	2	—
Shoulder, left	1	10	10	1
Shoulder, both	3	5	2	—
Arm, right	15	5	—	—
Arm, left	4	10	8	1
Arm, both	1	4	3	1
Back, in general	—	—	2	—
Back, interscapular	9	13	6	8
Back, right	—	—	3	—
Back, left	—	—	25	4
Flank, left	—	—	—	2
Epigastrium	—	7	11	2
Abdomen	9	—	10	12

the patient's statement for "chest-pain" being all that was recorded. The site of the sac accounts for the frequency of pain in the right chest in the ascending arch group, and in the left chest in the transverse, descending and thoracic aorta group. (Transverse arch aneurysms are found to point more often to the left than to the right.)

The greater frequency of precordial pain in the ascending arch cases may possibly be on the basis of more frequent involvement of the coronary orifices or aortic valvular incompetency. Regarding pain referred to the head, it is of interest that one patient had a mastoidectomy because of pain

referred to this region. Some textbooks call attention to the frequency of pain referred to the left shoulder and left arm, but state that pain referred to the right upper extremity is rare. This has probably been emphasized because it suggests angina rather than aneurysm. In 28 cases of ascending arch aneurysm pain was referred to the right shoulder or arm. Pain in the left arm or shoulder occurred in 18 of the descending arch cases. In the case of the transverse segment involvement, 12 had pain referred to the right and 15 to the left upper extremity. Thus it is seen that pain radiating to the right upper extremity is by no means rare. Pain was referred to the back infrequently except in the presence of descending arch aneurysms. Of this group, 31 or about one-fifth had pain in the left back, and over one-third of the descending thoracic group also had pain at this site, due to the tendency for the sacs to point posteriorly when arising from these segments. Abdominal pain occurred in over one-third of the descending thoracic segment group and was doubtless produced by segmental radiation due to pressure upon the lower intercostal nerves.

Dyspnea occurred more often than pain in some groups. It was present in practically 65 per cent of the ascending and transverse arch aneurysm cases. One-half of the descending arch and one-third of the descending thoracic cases showed breathlessness. Dyspnea is most often due to tracheal, bronchial or pulmonary compression.

Cough appeared in roughly one-half of the cases in each group with the exception of the aneurysms of the descending thoracic aorta. Sputum accompanied cough in about one-fourth to one-fifth of the cases. Cough and sputum are manifestation of pressure on the respiratory tract causing irritation and impaired drainage of secretions. Hemoptysis was found in a few cases and was, no doubt, associated with pressure upon trachea, bronchus or lung. At times, an aneurysmal sac eroding into the respiratory tract may ooze blood for days, before rupture occurs. Again, pressure may lead to bronchiectasis with which may be noted cough, sputum and hemoptysis. The congestion due to compression of the lung may lead to blood-streaked sputum. These three symptoms associated with fever and certain physical findings have frequently led to an erroneous diagnosis of pulmonary tuberculosis.

The incidence of hoarseness was greater in the transverse and descending arch aneurysms due to their relationship to the recurrent laryngeal nerve. However, a sac of the ascending arch, pointing upward, may lead to pressure on the right laryngeal nerve, a fact not generally recognized. This will be discussed later.

Dysphagia was found most often in the transverse arch group because of the intimate relationship to and pressure upon the esophagus.

Edema of the lower extremities occurred most often in the ascending arch cases because of the greater frequency of aortic insufficiency and congestive heart failure in this group.

Tracheal compression, causing "choking spells," was found more frequently in the case of sacs of the transverse arch because of the lessened opportunity of expansion of a sac in this location without compression of adjacent structures.

Vertigo, probably associated with abnormalities in the origin of the carotid arteries from the arch, appeared most often in the presence of aneurysm of transverse and ascending arch segments.

Miscellaneous symptoms, not noted in the table, will be briefly enumerated. Motor and sensory disturbances in the right arm occurred in four cases of ascending arch lesions. Edema of the face and neck appeared in two cases of ascending and in four cases of transverse arch aneurysms. Pulsation and bulging of the chest wall were occasionally noted by the patients. In two ascending, one descending arch and four descending thoracic segment cases, the aneurysm was accompanied by nausea and vomiting. Hematemesis was noted in one descending arch case. Swelling of the left shoulder was noted once in the transverse arch group as was swelling of the left arm in another. Aphonia occurred once, also in this group. Paraplegia was present in two descending arch cases.

Physical Signs

The physical findings are summarized in table 14. If the physician will recall the directions that an expanding aneurysmal sac may take, and the anatomical structures which may be pressed upon, the symptoms and signs become clarified.

Table XIV

Physical Signs in Aneurysms of the Thoracic Aorta

Physical Signs	Ascend. Arch (214 cases)	Trans. Arch (205 cases)	Descend. Arch (147 cases)	Descend. Thor. (30 cases)
Tracheal tug	14	22	7	1
Thrill	38	22	19	2
Diastolic shock	10	11	10	1
Pulsation, suprasternal	8	21	6	1
Pulsation, upper chest	—	4	—	—
Pulsation, rt. upper chest	33	—	—	—
Pulsation, lt. upper chest	—	9	14	1
Pulsation, supra-clavicular	4	—	—	—
Pulsation, neck	2	6	2	—
Pulsation, lt. interscapular	—	—	17	1
Retrosternal dullness	45	62	9	—
Dullness right of sternum	26	—	—	—
Cardiac enlargement	79	64	38	—
Systolic murmur at apex	96	64	60	11
Systolic murmur at base	59	35	21	4
Diastolic murmur at base	54	33	26	4
Aortic second accentuated	25	38	26	1
Signs of cardiac failure	30	21	11	1
Fever	42	49	37	7

Tracheal tug would be expected to be produced more often by sacs of the transverse and descending segments, but from the table it may be seen that, contrary to general teaching, this sign may also be produced by ascending arch sacs. This is true because at times sacs appear on the lesser curvature of the arch, and also because they may occasionally point to the left.

Thrills are felt more easily over those sacs which point externally, and this accounts for their frequency in ascending and transverse segment aneurysms. Diastolic shock was noted about equally in the groups. Pulsation and retrosternal dullness are so obviously related to the anatomical site and direction of pointing of the sac that it seems needless to discuss this more than to call attention to the table.

The diastolic murmur of aortic incompetency was noted in 25 per cent of the cases of the ascending arch sacs, whereas it was present in 16 and 17 per cent of transverse and descending arch aneurysms respectively, and in 13 per cent of descending thoracic aneurysms. This difference is to be expected because of the site of aortitis. Of the 117 cases with aortic insufficiency, 51 had a blood pressure higher than 140 mm. and of these 23 had a systolic pressure of over 160 mm.

Cardiac enlargement was recorded in 37 per cent of aneurysms of the first segment, 31 per cent of the second or transverse, and 25 per cent of the descending arch segment. These figures are probably not accurate since an error not uncommonly made in aneurysm of the aortic arch is the interpretation of downward and outward displacement of the heart as cardiac enlargement. Systolic murmurs at apex or base are difficult of interpretation from records. The former murmur is in many cases no doubt evidence of a relative mitral insufficiency accompanying a hypertrophied and dilated left ventricle. The signs of cardiac failure were found most often in the ascending arch group and associated with a regurgitant lesion of the aortic valves. Congestive heart failure is not a part of the picture of aortic aneurysm. In this series it occurred in 14 per cent of ascending, 10 per cent of transverse, 7.5 per cent of descending and 3.3 per cent of descending thoracic aortic lesions.

Because of the number of vital structures which may be compressed or distorted by an expanding aneurysmal sac a great variety of abnormal findings may be noted. (Table 15.)

In the circulatory system the most frequent effect of pressure is venous engorgement. This may be noted in the head, upper extremities and over the upper chest. Generally, it seems that sacs of the ascending and transverse arches have the most marked effect because they are so located as to most easily obstruct the venous return from head and arms. Edema of the face, neck and arms, and cyanosis were found in these two groups, as may be seen in table 12. Dilated veins of the upper chest and shoulders were also noted in the case of sacs arising from these segments of the aortic arch, in 12 to 13 per cent of each group. Occasionally one sees the most extreme

TABLE XV

Signs of Pressure Due to Aneurysmal Sacs

Signs	Ascend. Arch (214 cases)	Trans. Arch (205 cases)	Descend. Arch (147 cases)	Descend. Thor. (30 cases)
Edema, face and neck	3	4	1	—
Edema, right arm	2	1	—	—
Edema, left arm	—	5	—	—
Cyanosis, head and neck	1	4	—	—
Dilated veins, upper chest	22	28	—	—
Dilated veins, rt. shoulder and arm	5	—	—	—
Dilated veins, lt. chest and shoulder	—	—	19	—
Trachea deviated to right	4	7	1	—
Trachea deviated to left	3	1	1	—
Respiratory stridor	9	24	10	—
Esophagus, pressure (barium)	2	9	1	1
Pupils, unequal	4	2	4	1
Pupils, left dilated	3	8	4	—
Pupils, right dilated	2	2	1	—
Vocal cords, abnormal	7	10	—	1
Vocal cords, paralysis, left	1	6	8	—
Vocal cords, paralysis, right	2	—	—	—
Pulses unequal	4	1	3	—
Pulse, right weak	3	6	—	—
Pulse, right absent	4	2	—	—
Pulse, left weak	6	4	6	1
Pulse, left absent	1	7	—	—
Paralysis right arm	2	—	—	—
Compression myelitis, paraplegia	—	—	2	—
Exophthalmus, left	—	1	—	—

and exaggerated venous pattern over the chest with blood flow downward to anastomose with dilated veins over the abdomen.

Tracheal displacement must have been more common than was recorded in the case records, for in my experience it has been noted very frequently. Respiratory obstruction as made evident by stridor was met with most often in the transverse arch group, 12 per cent. Esophageal pressure as shown by barium was occasionally met with, again most often in transverse arch aneurysms.

Pupillary changes, dilatation or constriction, have been most often explained by pressure on the sympathetic chain. Wall and Walker [21] have attempted to explain such findings on the basis of inequality of the blood pressure. They found large pupils with low blood pressure, and constricted pupils with high pressure. Anisocoria was noted by them as due to unilateral change in pressure. In 26 cases of thoracic aneurysm they found a relationship between the pupils and the pressure. The findings in this series do not agree with such an idea, since dilation of the left pupil, the most frequent abnormality, was found six times with the blood pressure equal in both arms, and found in the presence of a higher pressure on the left side, and again with higher pressure on the right. There was no relationship between blood pressure differences in the two arms and type of pupil irregularity.

Weakness or paralysis of the vocal cords was recorded as listed in the table. As would be expected from the anatomical relations of the recurrent laryngeal nerve, the vocal cord abnormalities were manifest more often on the left than on the right side. But it should be pointed out that if the sac points upward in the case of ascending arch aneurysm, there may be sufficient distorsion of the right laryngeal nerve, where it loops about the subclavian artery, to lead to abnormality of the right vocal cord.

TABLE XVI

Data on Blood Pressure in Aortic Aneurysm

	Ascend. Arch	Trans. Arch	Descend. Arch	Descend. Thor.
BP recorded in	126	119	77	18
Of these, both arms	76	75	36	9
BP lower on right	10	6	5	—
BP absent on right	3	1	—	—
BP lower on left	9	22	12	—
BP absent on left	1	2	—	—
BP absent, both arms	—	1	—	—

Systolic and Pulse Pressures

Systolic Pressure	Number of cases	Aortic Insuf.	Pulse Pressure (within 5 mm.)	Number of cases
85 to 90 mm	3	1	12	1
			20	2
90 to 110 mm	60	4	15	7
			25	27
			45	21
			55	3
			70	1
			110	1
110 to 125 mm	55	9	25	8
			35	11
			45	27
			60	8
			80	1
125 to 140 mm	89	20	30	13
			45	32
			55	27
			75	12
			90	3
140 to 180 mm	128	45	45	21
			55	25
			65	27
			85	39
			112	11
			125	1
			150	1
180 to 220 mm	21	6	35	2
			60	1
			80	9
			95	6
			120–140	3
Over 220 mm	6	1	85	3
			110	3

The blood pressure was recorded in 340 or 57 per cent of cases. Readings in both arms were made in 196 or 57.6 per cent of those having had a determination made. The blood pressure was lower in the right arm in 21, and absent in four. It was lower on the left side in 43, and absent in three. On the left it was lowered most often in the presence of transverse segment sacs. A difference of less than 15 mm. was not considered significant. Bilateral absence of demonstrable blood pressure was found once. (Table 16.)

In table 16 are listed also, the data in general as regards the blood pressure findings. In 128 cases, or in 38 per cent of those having blood pressure records, the systolic pressure was from 140 to 180 mm. As was noted earlier, there were 117 instances of aortic insufficiency, of which 51 had a pressure of over 140 mm. Since there were 155 cases in which the systolic pressure was over 140 mm., it is seen that aortic regurgitation was present in only one-third of the individuals with hypertension.

Pulse inequalities and differences of blood pressure in the two arms, may be explained either on the basis of pressure by the sac upon vessels as they leave the arch, or by loss of pressure in arteries arising from an aneurysmal sac. In expansion of the sac some pressure is lost. Inequality or absence of the pulse on one side was found in 8 per cent of cases with a distribution as recorded in table 15. Complete bilateral absence of pulsation was not recorded once, though in one instance the pulse was extremely weak and the blood pressure could not be recorded. Bilateral absence of the radial pulse is a rare condition. In 1930, Kampmeier and Neuman [22] added a fourth such case to the only three which could be found in the literature.

Signs of pointing of an aneurysmal sac were either a localized bulging of the chest wall, with pulsation, or an expansile tumor projecting from or through the chest wall. The greatest number were found among the ascending arch group since aneurysms in this location tend to point anteriorly and to the right. There were 79 of these which constitute 37 per cent of the ascending arch aneurysms. Sixty-four or 31 per cent of the transverse arch aneurysms produced signs of a pointing sac. One-fourth of the aneurysms of the descending arch showed evidence of erosion through the chest wall, most often posteriorly. Table 17 gives in detail the sites of localized bulging or expansile tumors.

Roentgenologic Examination

The roentgen-ray was used in the study of each of the 44 cases of aneurysm of the Vanderbilt University Hospital series, and in 447 of the Charity Hospital cases. Aneurysm was diagnosed by this means in 471 of the total 633 cases.

The accuracy of the roentgen-ray examination may be seen by a comparison of the roentgen-ray and necropsy diagnoses. Of the 165 cases in

TABLE XVII
Site of Pointing Aneurysmal Sac

	Ascend. Arch (214 cases)	Trans. Arch (205 cases)	Descend. Arch (147 cases)	Descend. Thor. (30 cases)
Local bulging with pulsation				
Manubrium	—	6	—	—
Lt. sterno-clavicular	—	6	—	—
Rt. upper chest	17	2	—	—
Lt. upper chest	—	—	10	—
Lt. interscapular	—	—	2	2
Tumor, with pulsation				
Manubrium	—	18	—	—
Rt. sterno-clavicular	26	12	—	—
Suprasternal	1	—	1	—
Rt. upper chest	33	—	—	—
Lt. upper chest	2	17	11	—
Lt. neck	—	3	—	—
Lt. interscapular	—	—	11	4
Lt. lower chest, back	—	—	—	2

which postmortem examination was done, there were 75 in which roentgenologic study had been made. In 15 of the 71 Charity, and in 2 of the 4 Vanderbilt cases, the aortic lesion had been missed, or an error of 22.6 per cent of the cases coming to necropsy. In some of these, associated findings made the recognition of a sac impossible. For example, two of the Charity Hospital cases were diagnosed as having pleural effusion by the roentgenologist, and at necropsy this was found to be present, obscuring the aortic lesion. Similarly, massive collapse of the lung interfered with the delineation of a sac in one case. Other diagnoses in cases having aneurysmal sacs at necropsy were: "hilus shadow" in one, pulmonary tuberculosis in one, tumor of left lung in one, "density in left lung" in one, pneumonia of right lower lobe in one, and a shadow was described in two but not interpreted. There were five cases in which no abnormality was noted upon roentgen-ray examination, but in which aneurysmal sacs were found at necropsy.

Roentgenologic examination showed calcification in the aneurysmal sac in 11 cases. Erosion of sternum, clavicles and ribs anteriorly was recorded a number of times. This observation generally was of no assistance to the clinician, for in all cases an expansile bulging or tumor was visible. However, erosion of one or more vertebral bodies in sacs arising from the descending arch or descending thoracic aorta was demonstrated in some cases, and such findings were of great assistance in the evaluation of symptoms or signs. In the descending arch cases, there were nine in which erosion of one or more dorsal vertebrae occurred, from the third to eighth inclusive, and in three there was erosion of the posterior arcs of one or more ribs on the left side, from the fifth to eighth inclusive. Vertebral erosion by sacs of the descending thoracic segment was seen in five cases,

with involvement of one or more vertebrae from the sixth dorsal to first lumbar inclusive. In six, the posterior arcs of one or more of the left ribs, from the seventh to twelfth inclusive, were eroded. Among the 23 cases of multiple sacs, four showed erosion of vertebrae from the third to eighth dorsal, and erosion of ribs occurred in two cases. (There was a rare case of an ascending arch sac which eroded the fourth to sixth dorsal vertebrae on the right side, found at necropsy but not noted upon roentgen-ray examination.)

Cause of Death

Among the 633 cases of thoracic aortic aneurysm, 247 or 39 per cent died in the hospital. Necropsy was done in 165 cases or in 67 per cent of the deaths.

The causes of death, determined either clinically or at necropsy, are listed in table 18. Rupture of the aneurysmal sac occurred in 98 or in 39 per

Table XVIII

Cause of Death

Cause of Death	Arch	Ascend. Arch	Trans. Arch	Descend. Arch	Descend. Thor.	Multiple
Rupture, lt. pleura	—	1	1	6	8	1
Rupture, rt. pleura	—	3	—	3	2	—
Rupture, esophagus	—	2	6	8	1	2
Rupture, trachea	—	—	3	5	—	—
Rupture, external, skin	—	2	2	—	—	—
Rupture, pericardium	—	6	—	—	—	—
Rupture, respiratory, site not known	2	—	2	5	—	—
Rupture, mediastinum	—	1	2	—	—	1
Rupture, lt. bronchus	—	2	—	2	—	—
Rupture, rt. bronchus	—	2	—	—	—	1
Rupture, esophagus and lt. bronchus	—	—	—	—	1	—
Rupture, lt. upper lobe	—	—	—	2	1	1
Rupture, rt. upper lobe	—	—	—	1	—	—
Rupture, stomach	—	—	—	1	1	—
Rupture, esophagus and lt. pleura	—	—	—	1	—	—
Rupture, abdominal cavity	—	—	—	1	—	—
Rupture, adhesions of lt. lung	—	—	—	1	—	—
Rupture, pulmonary artery	—	—	1	—	—	—
Rupture, of abdominal aneurysm	—	—	—	1	—	—
Respiratory obstruction	3	9	25	8	—	1
Cardiac failure	2	15	5	3	2	2
Heart block	—	1	—	—	—	—
Angina pectoris	—	—	1	—	—	—
Coronary closure by pressure of aneurysmal sac	—	1	—	—	—	—
Pneumonia	—	9	9	3	—	2
Edema of lungs	—	4	1	—	—	—
Pulmonary infarct	—	—	—	1	—	1
Miliary lung abscesses	—	—	1	—	—	—
Tuberculosis of lung and pericardium	—	—	—	—	—	1
Acute nephritis	—	1	—	—	—	—
Carcinoma of prostate	—	—	—	1	—	—
Lt. hemiplegia	—	2	—	—	—	—
Cause unknown	1	13	12	7	3	2
Total	8	74	71	60	19	15

cent of the deaths. Respiratory obstruction was the next most common cause of death, occurring in 46 (18 per cent), over half of which were in cases of transverse arch aneurysms. Cardiac failure as a cause appeared next with 29 (11.5 per cent) such instances. Pneumonia, probably due to bronchial obstruction, led to death in 23 cases, or 9 per cent. As may be seen in the table, a variety of causes of death appeared in isolated instances.

Cases of Multiple Aneurysmal Sacs

More than one sac was described upon roentgen-ray examination or at necropsy in 23 cases of the series. Eight of the cases came to necropsy, and of these five had two sacs and three showed three sacs.

The duration of symptoms was no more than one month in two cases, one to three months in four cases, three to six in three cases, six to nine in three cases, and nine to 12 months in six cases. Three were of more than a year's duration, and in two no history was given.

Though no syndrome can be set up for a given combination of sacs, the clinician should not neglect to keep multiplicity of sacs in mind in the presence of symptoms inexplicable upon the basis of one sac. Incidentally, the roentgen-ray examination was fairly accurate in its diagnosis in this group.

Prognosis

With comparatively few exceptions, the duration of life, after the onset of symptoms in aneurysm of the thoracic aorta, is to be measured in months. Table 19 has been compiled to show the duration of symptoms in fatal cases. The small group of multiple aneurysm cases which died have not been included for in some it was not known which sac led to the fatal issue.

Table XIX

Time Elapsed from Onset of Symptoms to Death

	Ascend. Arch	Trans. Arch	Descend. Arch	Descend. Thor.
Less than 1 wk.	—	3	1	—
2 to 4 wks., inclusive	2	6	4	—
2 to 3 mo., inclusive	10	11	10	5
4 to 6 mo., inclusive	11	17	11	3
7 to 9 mo., inclusive	11	8	7	1
10 to 12 mo., inclusive	2	1	6	—
13 to 18 mo., inclusive	7	7	4	4
19 to 24 mo., inclusive	9	5	2	2
3 yrs.	6	1	3	1
4 yrs.	1	—	—	1
6 yrs.	1	—	1	—
14 yrs.	—	1	—	—
15 yrs.	1	—	—	—
"Years"	1	—	—	—
No history	12	11	11	2
Total	74	71	60	19

In arriving at averages for the various groups of cases, only those which gave a duration of symptoms of two years or less were chosen. It was felt that cases of longer standing are too few to be included for accuracy.

Generally it may be said that aneurysms of the transverse arch present the poorest prognosis as regards duration of life from the onset of symptoms. The average time elapsed from onset of symptoms to death in this group was 6.4 months. Descending arch aneurysms gave an average duration of the same length, 6.3 months, and aneurysms of the descending thoracic aorta, 8 months. These time intervals are not believed to be accurate indicators of the total duration of the lesions in these locations. Sacs of the descending arch and descending thoracic aorta are known to exist and remain asymptomatic for some time. The ascending arch aneurysms offer a slightly better prognosis. In this group the average duration of symptoms was 8.9 months. This is believed to be a possible indication of the duration of the lesion for it is in this group, as well as in the transverse arch group, that symptoms or signs become manifest early. However, it seems probable that the figures given are of little significance as regards the duration of the lesion.

Occasionally cases are found with a history of exceptionally long duration. One is inclined to discount these as mistakes in history taking or diagnosis. However, it is known that in rare instances aortic aneurysms may develop a "healed sac," by which is meant the building up of a strong wall of laminated clot, often infiltrated with calcium, which greatly retards the expansion of the sac. I have seen a patient with a calcified sac whose aneurysm had been diagnosed 13 years before, by the late P. M. Hickey, roentgenologist. In the present series one individual had experienced symptoms for 14 years and gave a history of a protruding mass for 7 years. Another patient gave a 15 year history and insisted that the protruding tumor had been present that length of time. The roentgen-ray examination revealed calcification in the sac.

Symptom Complexes

Aneurysm of the thoracic aorta stands second to none in interest from the standpoint of medical diagnosis. The quotation from Osler at the beginning of the paper indicates the diagnostic challenge this entity offers. Not only may aneurysm simulate many different diseases, but it also may attain immense size, and yet remain clinically silent, its presence attested to only by roentgen-ray examination or necropsy. Even after its roentgenologic revelation, a searching physical examination may still fail to elicit a single physical sign of its presence. Nevertheless, on the basis of this study, it is felt that very often, probably in most cases, either a definite or tentative diagnosis of aortic aneurysm can be made on the basis of symptoms and physical signs. If the less common symptoms and signs are noted and kept in mind and the roentgen-ray freely used, the diagnosis may be correctly arrived at even in extremely atypical instances.

The roentgen-ray examination is the most valuable aid in the diagnosis of aneurysm, but not to be used to the exclusion of the interpretation of clinical findings. It is only necessary to recall the 22 per cent of erroneous roentgen-ray diagnoses in the necropsy studies of this series. These mistakes, it must be remembered, occurred in institutions where the staffs are 'aneurysm conscious.' As has been convincingly demonstrated to me time and again by Dr. Amédée Granger, plates taken in the oblique positions, and especially in the left oblique, are of extreme value in the proper visualization of the aortic arch. These may show small aneurysms which might be missed at fluoroscopy. The examination with the fluoroscopic screen has long been considered the best means of diagnosing aneurysm because pulsations may thus be visualized. This is to be seriously questioned. It is not an infrequent occurrence to visualize a non-pulsating aneurysmal sac (organized clot) and it is extremely difficult to distinguish transmitted "pulsations" in solid tumors from the true expansile pulsation of aneurysm.

Finally, the clinician must use judgment based upon clinical findings in addition to whatever help the roentgen-ray may give. But he should not be so dependent upon the roentgen-ray that it will be allowed to exclude the diagnosis of aneurysm, else he will never have the satisfaction of seeing his clinical diagnosis of small aneurysmal sacs of the lesser curvature of the aorta established at the necropsy table. Sacs no larger than an egg at such a site may give clear-cut clinical signs but be absolutely invisible by any type of roentgen-ray study.

Symptom complexes which may be simulated by aortic aneurysm are varied and fairly numerous. It may be of interest to discuss some of these briefly.

Tuberculosis of the Lung. This is probably the most frequent diagnostic error, and occurs more often, I believe, in the case of descending arch aneurysms. Sacs at this site, because they are not superficial, may exhibit no pulsation. Their location is such that they may compress the left upper lobe, or may press upon a bronchus communicating with the upper lobe. Cough, sputum and weight loss suggest the diagnosis of tuberculosis. The presence of limitation of movement of the left upper chest, an impaired percussion note, crepitant and subcrepitant râles and fever add to the confusion. Blood streaks in the sputum due to compression and stasis in the lung or from slight oozing, may occur and all but complete the clinical picture of tuberculosis. The absence of tubercle bacilli in the sputum excites suspicion and a careful roentgen-ray examination may prove the only means of diagnosing an aneurysm of the descending arch of the aorta.

Bronchiectasis. Partial occlusion of a bronchus by compression is not an infrequent cause of bronchiectasis, and an aneurysmal sac may be the occluding agent. This is usually unilateral and the picture may be that of typical bronchiectasis. Stridor heard over one lobe, however, is suggestive of occlusion. The roentgen-ray may be the only means of establishing the cause of the bronchial lesion, though a small sac arising from the lesser

curvature of the arch may be so placed as to obstruct the left main bronchus and be invisible on roentgen-ray examination.

Pneumonia or Delayed Resolution. Similarly, obstruction in the respiratory tract may lead to the development of pneumonia. The history may be suggestive of the presence of this disease and subsequently the clinical picture may be that of delayed resolution resulting from improper drainage of secretion from the obstructed lobe.

Bronchogenic Carcinoma. The diagnosis of carcinoma is suggested when a middle-aged person complains of chest pain, ineffectual cough, some dyspnea and blood-streaked sputum. An aneurysmal sac eroding a major bronchus may produce these symptoms. There may be signs of atelectasis with either carcinoma or aneurysm. In passing, it is noteworthy that the most impressive tracheal tug I have ever felt occurred in a case of carcinoma of the left bronchus which had extended through the bronchial wall to involve the aorta in a mass of malignant tissue.

Sarcoma of Lung. In one of my cases there was dyspnea, cough, and edema of the right arm and shoulder. Over the right chest was widespread collateral circulation. Dullness with greatly suppressed breath sounds was present over the upper portion of the right lung. Marked pulsation in the second right interspace seemed to confirm the suspicion of aneurysm. At necropsy a huge sarcoma of the right upper lobe was found.

Laryngitis. Not uncommonly the patient with aneurysm visits an otolaryngologist because of hoarseness. Examination reveals paresis or paralysis of a vocal cord. A search for intra-thoracic disease is indicated, including a careful examination for aneurysm of the aorta.

Carcinoma of the Esophagus. In the case of several patients included in the series which has been presented, a tentative diagnosis of neoplasm of the esophagus had been made. Transverse and descending arch sacs may so press upon the esophagus as to lead to obstruction. Only upon fluoroscopy with or without barium in the esophagus, may the real cause of dysphagia be found.

Arthritis. Pain in the shoulder, especially on the right, in ascending arch aneurysm, may by its character and aggravation on active and passive motion simulate chronic arthritis.

Tumors of Thyroid and Thymus. An aneurysmal sac may so closely simulate an enlarged substernal thyroid as to lead to operation. If a thick lamellated clot is present, there is no pulsation, and the sac may be situated so that plates taken in the oblique positions will not show the aortic origin of the mass.

Mediastinal Tumors. Enlargement of the mediastinal lymph nodes, as occurs in Hodgkin's disease or lympho-sarcoma, offers diagnostic difficulties, clinical as well as roentgenological. Fluoroscopy for pulsation cannot always be depended upon for differentiation. Roentgen-ray plates made in the oblique position are of great value in determining the aortic origin of mediastinal tumor.

Mediastinitis. This may be syphilitic, but the character of the mediastinal shadow is not likely to be confused with a saccular lesion.

Spinal Cord Tumor. An aneurysmal sac eroding into the spinal canal may cause paraplegia and thus lead to the diagnosis of cord tumor. Especially is this likely to occur in sacs of the descending aorta.

Summary

1. The historical background of aortic aneurysm has been briefly reviewed.

2. From 1113 records of cases diagnosed as aortic aneurysm at the Charity and Vanderbilt University Hospitals, 633 have been selected for clinical analysis.

3. The incidence of aneurysm in this country and abroad has been considered.

4. Cases of saccular aneurysms of the four divisions of the thoracic aorta have been studied with respect to their clinical manifestations.

5. Prognosis has been briefly considered.

6. The causes of death in 247 patients have been summarized.

7. Problems in the differential diagnosis of saccular aortic aneurysms have been discussed.

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LIVER FUNCTION IN HYPERTHYROIDISM AS DETERMINED BY THE HIPPURIC ACID TEST *

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It has long been accepted that the liver undergoes pathologic changes in hyperthyroidism. A clinical manifestation of this liver damage is the occasional presence of jaundice of the hepatic type. Cameron and Karunaratne [1] in a recent review of the subject (1935) gave Paul the credit for reporting the first case showing the association of liver injury with hyperthyroidism. He (Paul, 1865) described the case of a woman of 33 years with Graves' disease of four years' duration, who showed cirrhosis of the liver at postmortem examination. Other early observers of this relationship were Habershon (1874) [2] who noted in a patient with exophthalmic goiter the occurrence of progressive jaundice 10 days before death; and Eger (1880),[3] Sutcliff (1898),[4] and Eder (1906),[5] all of whom observed jaundice in cases of hyperthyroidism.

Structural Changes in the Liver

Cameron and Karunaratne collected from the literature 242 cases in which the liver showed change on postmortem examination of cases of hyperthyroidism. They added 30 cases of their own. Haban [6] in 1933 studied 26 cases of such hepatic involvement and divided them into two groups: (1) Those with venous stasis (8 cases); and (2) those with changes independent of stasis (18 cases). In the latter group he recognized cases with fatty degeneration and infiltration, others with outstanding liver cell necrosis resembling yellow atrophy and another group of cases for which he suggested the term "cirrhosis basedowiana." Weller [7] (1933) paid especial attention to the more chronic changes in the liver. He found what he called patchy chronic parenchymatous interlobular hepatitis in 65 per cent of his cases of exophthalmic goiter and in only 2 per cent of a control series. He noted that the changes which he found in the liver in cases of exophthalmic goiter differed from the changes seen in cirrhosis; they were irregularly distributed; many lobules appeared normal. There was also less proliferation of bile ducts. He also noted areas of necrosis still present in the parenchyma.

Rössle [8] in 1933 divided his group of 30 cases into those showing acute or recent changes such as central and perivenous necrosis, and those with chronic changes. The changes were most marked at the edge and surface of the liver. Beaver and Pemberton [9] in 1933 distinguished three types of histologic change in their cases: (1) acute degenerative in 91 per cent;

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(2) simple atrophy in 64 per cent; and (3) subacute toxic atrophy and toxic cirrhosis in 60 per cent of the cases. The severity of the hyperthyroidism was the determining factor in the degree of pathological change.

Cameron and Karunaratne recognized three types of changes in the liver: (1) Cases with acute damage; (2) cases with evidence of progressive damage; and (3) arrested cases.

A reduction in the weight of the liver in hyperthyroidism as evidence of liver damage has been mentioned in the literature. The average liver weight of three large groups of cases (chart 1) totaling 167 cases was found

CHART I

Mean Weights of Normal Livers and Hyperthyroid Goiter Livers

	Number of Cases	Mean Liver Weight
NORMAL	50	1424 Grams
1. Rössle	30	
2. Cameron and Karunaratne	30	
3. Beaver and Pemberton	107	
Total Combined Series	167	1232 Grams

to be 1232 grams. The average weight of 50 normal livers, compiled by Boyd [10] was found to be 1424 grams. The average liver weight of seven patients dying in thyroid crisis at the Lahey Clinic was 1407 grams; all were within the limits of normal.

FUNCTIONAL CHANGES IN THE LIVER

Studies of hepatic function in hyperthyroidism have been carried out by a number of investigators. Hirose [11] in 1912 found that patients with hyperthyroidism had a high value for alimentary galactosuria similar to that found in hepatic cirrhosis and catarrhal jaundice. In 1922 Sanger and Hun [12] studied the blood sugar curve after giving glucose to normal persons and to patients ill with hyperthyroidism. Abnormal curves were found in hyperthyroidism and attributed to a failure of the liver to store glucose.

Youmans and Warefield [13] in 1926 studied the liver function in 44 cases of thyrotoxicosis mainly by means of the phenoltetrachlorphthalein test. They reported that 50 per cent of the patients in the entire series showed an impairment of the liver function according to the tests used. Kugelmann [14] in 1930 reported the results of studies of the blood sugar curves of normal individuals and of patients with hyperthyroidism, following the feeding of levulose. He concluded that in this disease the liver had lost the capacity to transpose levulose to dextrose and to store it.

Heilmeyer [15] in 1931 found the urobilin quotient elevated in three of six cases with hyperthyroidism. The power of the liver to eliminate bilirubin was impaired in each of a group of five cases. Lichtman [16] found a disturbance in the oxidation of cinchophen in 16 cases of uncomplicated hyperthyroidism. This he reported as indicating moderate impairment of

the capacity of the liver cells to oxidize this substance. No evidence of severe impairment was reported and no relationship was noted between the degree of functional liver change and level of the basal metabolism, duration of disease or degree of weight loss.

Maddock, Coller, and Pedersen [17] studied the liver function by means of the dye test and determination of serum bilirubin. Of 13 patients with toxic goiter, 8 or 61 per cent showed evidence of liver damage before operation. A relationship was found to exist between the severity of the disease and the degree of liver damage. Althausen and Wever [18] in a recent study reported an abnormal elevation of the galactose content of the blood after the oral administration of this sugar. After thyroidectomy the galactose tolerance returned to normal.

The Takata and Ara reaction was studied by Ragins [19] who found in two cases of exophthalmic goiter and in one of toxic adenoma that there was a four plus reaction, in one case of toxic adenoma a three plus reaction and in two cases of exophthalmic goiter a one plus reaction. There was a negative reaction in seven cases of exophthalmic goiter and in one of toxic adenoma.

These clinical and pathological observations conclusively demonstrate that the liver frequently suffers damage in hyperthyroidism. In addition, work by Heyd,[20] Boyce,[21] and Sutton [22] suggests that the hyperthermic reaction which occasionally follows operations on the bile ducts, pancreas, and thyroid is related to disturbances in the liver. Death in these cases has been termed "liver death." The typical reaction is characterized by sudden, rapid and progressive rise in the temperature during the first day after operation, falling blood pressure, rapid pulse, circulatory collapse, and coma The temperature may reach 107 to 108 degrees within 36 to 48 hours.

With all this evidence at hand to show the increasing importance of the liver in hyperthyroidism a study was planned to investigate this subject, by a new method.

Method of Determination of Liver Function

The liver function was determined by the hippuric acid excretion test suggested by Quick.[23] The test is based on the assumption that the liver is concerned with the conjugation of benzoic acid and glycine to form hippuric acid. When a normal individual takes 6 grams of sodium benzoate by mouth, 3 grams of hippuric acid are excreted in the urine in four hours. The test has received clinical trial by Quick, Vaccaro,[24] Snell and Plunkett,[25] and Kohlstaedt and Helmer [26] and has been found to be a moderately satisfactory test for the determination of parenchymatous hepatic damage. The accuracy of the test compares favorably with that of other hepatic function tests. The simplicity of the test and the low cost of chemicals used in the determination are definite advantages.

Material

This study is based on the results of liver function determinations in 148 cases of clinical hyperthyroidism, all of which came to operation. Seventy-eight cases had primary hyperthyroidism permitting a subtotal thyroidectomy, 39 cases had primary hyperthyroidism requiring a two-stage operation, and 31 cases had adenomatous goiter with hyperthyroidism permitting a subtotal thyroidectomy. Liver function determinations were obtained periodically as follows: On the day after admission; on the day prior to operation (8 to 14 days being taken for preoperative treatment); and

TABLE I

Hippuric Acid Excretion in Primary Hyperthyroidism
(One stage operation)

Case	Age	Sex	Weight change, pounds	Duration of disease, months	Iodine prior to admission	Basal rate			Liver function			3 months check-up	
						On adm.	6th day	Post-op.	On adm.	Pre-op.	Post-op.	Basal rate	Hippuric acid
1	30	F.	Loss, 20	2	0	+49	+21	0	2.16	2.84	2.55		
2	37	F.	Loss, 30	24	0	+41	+31	+ 7	2.22	1.93	2.65		
3	22	F.	None	2	0	+18	+ 7	+22	2.62	3.20	2.28	− 5	3.97
4	32	F.	Loss, 10	5	0	+44	+19	+ 6	1.07	2.32	1.32	−15	3.27
5	32	F.	Loss, 19	5	0	+26	+16	− 6	2.45	2.88	2.58	− 8	3.01
6	31	F.	Loss, 4	5	0	+46	+25	+19	1.75	2.45			
7	35	M.	Loss, 25	12	2 wks.	+26	+16		2.26	2.96	1.42	+ 3	3.16
8	31	F.	Loss, 10	15	0	+44	+25	+ 9	1.13	3.08			
9	33	F.	None	8	0	+49	+27		2.96	2.82	2.52	− 2	3.19
10	28	F.	None	12	0	+27	+23	− 8	2.54	2.26	1.69		
11	56	M.	Loss, 20	4	0	+45	+20	+18	2.45		2.16		
12	24	F.	Loss, 5	12	2 wks.	+25	+16		1.98	3.28	2.54		
13	39	F.	Loss, 12	12	0	+17	+16		2.83	2.94		+ 5	3.13
14	42	F.	Loss, 42	18	10 days	+23	+ 6	+ 5	2.03	2.07	1.83	− 9	2.67
15	36	F.	Loss, 29	1	0	+32	+24		1.70	1.62	1.80		
16	20	F.	Loss, 45	6	0	+24	+ 9	0	2.41		3.33		
17	26	F.	None	24	0	+56	+29	+ 1	2.61	1.73		−23	2.50
18	40	F.	Gain, 14	18	1 wk.	+28	+17	+21	2.16		3.07		
19	32	F.	Loss, 9	4	0	+24	+25	+29	2.95	2.91		0	2.99
20	23	F.	Gain, 8	6	0	+29	+22		2.96		2.83		
21	45	F.	None	10	0	+49	+30	+23	2.90	3.20		− 1	3.55
22	25	F.	Gain, 9	12	5 mos.	+68	+29	+28	2.50	2.17	2.72	+ 2	3.02
23	40	M.	Loss, 50	24	2 yrs.	+56	+31	+46	3.48	3.52	3.61		
24	49	F.	Recent gain	36	0	+12	+13	− 5	2.56		2.33	+17	3.79
25	23	F.	Gain, 10	12	0	+39	+ 9	− 6	3.03	2.92	3.03		
26	48	F.	Loss, 30	8	0	+30	+16	+16		2.75	3.02	−19	4.61
27	61	F.	Loss, 20	12	0	+18	+12			1.61			
28	29	F.	None	18	13 mos.	+22	+29		2.17				
29	52	F.	None	4	0	+32	+15		2.58		0.55	− 7	2.14
30	52	F.	None	2	0	+30	+14	+ 6	0.98	1.22	1.10		
31	23	F.	Gain, 8	6	0	+29	+22		2.96		2.83		
32	37	F.	Loss, 16	24	0	+35	+18	+15	1.77			0	3.83
33	59	F.	Loss, 12	6	6 mos.		+ 8	+ 7		2.84		−22	3.33
34	52	F.	Loss, 25	120	9 mos.	+43			1.09		0.54		
35	30	F.	Loss, 15; Rest gain	7	0	+37	+14	0	2.28		2.20		
36	32	M.	Gain, 8	12	0	+42	+21	+21	3.43		3.84		
37	47	F.	Loss, 25	4	4 mos.	+39	+18	+17	3.11		2.71		

TABLE I (*Continued*)

Case	Age	Sex	Weight change, pounds	Duration of disease, months	Iodine prior to admission	Basal rate			Liver function			3 months check-up	
						On adm.	6th day	Post-op.	On adm.	Pre-op.	Post-op.	Basal rate	Hippuric acid
38	29	F.	Gain, 50	9	0	+30	+24			3.43	3.00		
39	48	M.	Loss, 26	12	0	+37	+45	+23	2.83	3.05			
40	30	F.	None	18	0	+36	+28	+16	2.99	2.12			
41	39	F.	None	1	0	+33	+12			3.79			
42	25	F.	Loss, 20	3	0	+56	+18			2.51			
43	50	F.	Loss, 28	18	5 wks.	0				2.34			
44	34	M.	Loss, 19	24	0	+30	+16		3.73	3.47			
45	55	F.	Loss, 2	18	1 yr.	+ 2				1.69			
46	35	F.	None	6	0	+16	+15			3.40			
47	24	M.	Loss, 23	12	0	+40	+19	− 7	2.62	3.11			
48	48	M.	Loss, 25	10	0	+29	+12		3.33				
49	32	F.	Loss, 25	4	0	+48	+34			2.52			
50	23	F.	Loss, 9	12	0	+56	+45		1.00	2.03	2.11		
51	16	F.	Gaining	1	0	+40	+16		2.81				
52	42	F.	Loss, 5	2	2 mos.	+43	+30		3.03				
53	40	M.	Loss, 43	5	0	+54	+30		1.84	1.38			
54	36	F.	Loss, 35	12	0	+44	+20		1.59				
55	35	F.	Loss, 9	6	0	+29	+20		2.09				
56	36	F.	Loss, 20	4	0	+62	+22		2.18	3.18			
57	39	M.	Loss, 5	18	1 wk.	+19		+12	2.37				
58	57	M.	Loss, 15	24	7 mos.	+36	+17	−14		1.71	2.60	+ 7	3.12
59	43	M.	Loss, 25	9	10 days	+12			2.39	3.34	3.56		
60	22	F.	Gaining	24	6 mos.	+41	+17	+16	3.73	3.41			
61	38	F.	Loss, 10	12	0	+25	+14		1.65				
62	46	M.	Gaining	8	0	+58	+27		1.65	2.87	2.30		
63	38	M.	Loss, 30	18	0	+34	+32		2.77	3.13			
64	45	F.	Loss, 12	36	0	+37	+10		2.12	1.72			
65	46	F.	Loss, 12	10	0	+38	+11		2.00	1.71			
66	39	M.	None	5	0	+52	+32	+ 7	1.66	2.91			
67	43	F.	Loss, 20	60	0	+66	+54	+35			1.83	+ 2	3.80
68	51	F.	Loss, 28	2	0	+62	+35		1.28	2.88		+33	2.77
69	33	F.	Loss, 24	4	2 wks.	+56	+57		2.54			−13	3.08
70	52	F.	None	2	0	+24		+28	3.70				
71	19	F.	Loss, 7	0.5	0		+16	+ 5		2.03			
72	42	F.	Loss, 6	12	3 wks.	+20	+13	+ 7	2.28		2.96		
73	53	M.	Loss, 20	2.5	0	+34	+17		0.91	1.33			
74	37	F.	Loss, 14	12	10 days	+13				2.59			
75	19	F.	Loss, 9	8	0	+41	+19		0.65	1.90			
76	38	F.	Loss, 6	1	0	+30	+39		3.53				
77	36	F.	Loss, 6	3	0	+50	+42		0.04	1.43			
78	22	F.	None	12	1 mo.	+52	+45		1.94				

on the sixth or seventh day postoperatively. The cases requiring a two-stage operation had determinations prior to the second stage (six weeks usually elapsing between operations) and on the sixth or seventh day postoperatively. All the cases did not have the entire series of tests. Determinations were again obtained in 42 cases three months postoperatively when they returned for their usual three months metabolic check up.

RESULTS

In the group of 78 cases (table 1) whose primary hyperthyroidism was of sufficient clinical mildness to permit a subtotal thyroidectomy, the aver-

age hippuric acid excretion on admission was found to be 2.30 grams (chart 2). The average admission basal metabolic rate was plus 36 per cent. Of the entire group, only 15 per cent, i.e. 10 cases (Nos. 23, 25, 36, 37, 44, 48, 52, 60, 70, 76), had determinations above the accepted normal of three

CHART II

Hippuric Acid Excretion in Primary Hyperthyroidism
(One-stage operation)

No. Cases	Average B.M.R. %				Average Hippuric Acid Excretion in Grams			
	On Adm.	On 6th Day	Postop.	3 Mos. Check Up	On Adm.	Preop.	Postop.	3 Mos. Check Up
78	+36	+22	+11	−3	2.30	2.55	2.39	*3.34
Percentage of normal hippuric acid determinations					15%	29%	23%	85%

* 2 cases of myxedema and 1 recurrent case not included in the determination.

grams. Eight of this number had either had iodine before admission or had not suffered weight loss; and in these eight these factors were considered the basis for the normal hippuric acid excretion. After the usual preoperative period the average hippuric acid was 2.55 grams and the average basal metabolism plus 22 per cent. Although the increase in the average hippuric acid excretion was relatively small, at this point 29 per cent of the cases had normal hippuric acid excretions. Postoperatively the average hippuric acid excretion was 2.39 grams with 23 per cent of the cases having normal excretions. Three months postoperatively the average basal metabolic rate was minus 3 per cent and the average hippuric acid excretion was 3.34 grams, with 85 per cent of 20 cases now having normal excretions. In calculating this average, two cases of clinical myxedema and one case of recurrent hyperthyroidism were excluded (Nos. 17, 29, and 68).

In the group of 39 cases of primary hyperthyroidism (table 2) having the disease with sufficient clinical severity to require a two-stage operation the average basal metabolic rate was plus 54 per cent and the average hippuric acid excretion 1.88 grams (chart 3). On admission only one case (No. 37) had a normal value for the hippuric acid excretion; that happened to be in a case having an associated pregnancy. Preoperatively to the first stage the basal metabolic rate fell to an average of plus 36 per cent and the average hippuric acid excretion increased to 2.33 grams with 20 per cent of the cases now showing normal determinations. Postoperatively a slight drop occurred in the average hippuric acid excretion. Now, however, only 7 per cent had normal hippuric acid determinations. At the time of the second stage the average basal metabolic rate was plus 21 per cent with

TABLE II

Hippuric Acid Excretion in Primary Hyperthyroidism (Two stage operation)

Case	Age	Sex	Weight change, pounds	Duration of disease, months	Iodine prior to adm.	First stage						Second stage				3 months check-up	
						Basal rate, per cent			Hippuric acid, in grams			Basal rate, per cent		Hippuric acid, grams			
						On adm.	On 6th day	Post-op.	On adm.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Basal rate	Hippuric acid
1	31	F.	Gain, 6	18	6 mos.	+88	+81	+32	1.41	2.93	2.12	+41	+24	2.35	2.19		
2	32	F.	Loss, 35	10	0	+47	+30	+15	0.93	1.52	1.72	+23	+ 3	2.09	2.20	−30	2.16
3	27	F.	None	24	0	+76	+51	+36	2.31	2.79	2.05	+20	+ 6	2.86	2.91	+ 5	3.00
4	30	F.	Loss, 13	8	0	+99	+55	0	0.92	1.37		+60	+17	1.67		+31	0.93
5	36	F.	Loss, 17	6	0	+44	+38	+12	1.35	2.26	1.82	+16	+ 4	2.52	2.62	− 4	3.16
6	24	F.	Loss, 20	7	0	+76	+23	+14	2.03	2.24	2.45	+42	+24	2.38	1.96	+37	2.09
7	60	F.	Loss, 25	24	1 yr.	+37	+36	+28	2.40	2.70	2.20	+11	+ 2	3.0	1.85		
8	55	F.	Loss, 32	4	0	+66	+43	+20	1.65	2.60	2.04	− 2	+ 4	2.55	3.10		
9	43	F.	Loss, 20	3	0	+44	+43	+27	2.24	2.39	1.88	+16		2.41	1.46	−13	2.73
10	62	F.	Loss, 20	4	0	+32	+37	+36	2.18		1.40	+ 8	+11	2.18	2.51	− 6	3.08
11	46	F.	Loss, 20	8	0	+15	+26	+16	1.98	1.26	1.88	+14	+12	2.38	1.64		
12	46	F.	Loss, 20	3	0	+56	+24		1.28	1.58	1.99	+42	+ 9	1.70	3.73		
13	55	F.	Loss, 40	7	1 wk.	+60	+33	+34	1.31		2.26	+29	+12	2.47	3.21		
14	45	F.	Loss, 3	3	3 mos.	+37	+28	+31	0.76	1.73	2.09	+28	+10	1.27		+11	2.34
15	38	F.	Loss, 23	9	0	+71	+53	+42	1.75	2.14	2.35	+44	− 5	2.61			
16	53	F.	Loss, 50	24	0	+42	+28	+ 9	2.82	3.05	2.15	− 1	− 6	3.38	3.13	+ 5	4.00
17	44	F.	Loss, 40	2	5 days	+34	+31	+17	2.65	3.22	3.53	+14	+ 7	3.57			
18	16	F.	Loss, 10	12	1 yr.	+85	+42	+20	2.64	2.75		+36	+12	2.31			
19	54	M.	Loss, 50	14	0	+63	+51	+44	2.24	1.83		+61	+33	0.97		−25	3.45
20	55	F.	Loss, 80	48	0	+21	+13	+10	1.49	1.22	2.49	− 2	+ 3	1.94			
21	33	F.	Regain 5 of 20 lost	1.5	5 wks.	+94	+43	+28	1.69	2.08	1.97	+21	+ 7	2.58			

TABLE II—*Continued*

Case	Age	Sex	Weight change, pounds	Duration of disease, months	Iodine prior to adm.	First stage						Second stage				3 months check-up	
						Basal rate, per cent			Hippuric acid, in grams			Basal rate, per cent		Hippuric acid, grams			
						On adm.	On 6th day	Post-op.	On adm.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Basal rate	Hippuric acid
22	16	F.	Loss, 14	12	5 wks.	+33	− 4	+ 6	1.42	1.45	2.54	+ 9	− 8	2.27		−14	2.67
23	42	F.	Loss, 20	6	5 mos.	+79	+55	+32		3.16	2.90	+19	+10	3.50	3.50	−18	3.00
24	50	F.	Loss, 14	6	4 mos.	+69	+32	+18	0.84		1.94	+26	+14	2.05			
25	57	M.	Loss, 45	24	6 mos.	+22	+ 6	+16	2.39	3.11		0		1.88			
26	34	F.	Loss, 20	10		+67	+34	+25		2.99		+26	+ 6	2.60	3.13	−13	3.00
27	54	F.	Loss, 30	24	6 mos.	+29	+25	+16	2.39			+25		2.62			
28	41	F.	Loss, 3	48	2 yrs. None for 3 mos.	+62	+38	+26	2.54	2.33		+10	− 6	3.65			
29	43	F.	Loss, 22	30	8 mos.	+53	+52	+30	2.07	3.02		+26	+20	2.84			
30	40	F.	Loss, 4	36	0	+26	− 5	+11	2.28	2.27		+25	+12	3.06			
31	24	F.	Loss, 20	14	0	+67	+34	+25	2.58			+15		3.86			
32	38	F.	Loss, 20	3	0	+43	+34		0.89	1.83		+23		2.46			
33	48	F.	Loss, 53	36	0	+65	+53		1.51	3.36	2.94	+20		3.35			
34	50	F.	Loss, 30	48	0	+55	+31	+33	2.29		1.92	0	+ 5			−15	3.91
35	29	M.	Loss, 35	12	0	+48	+29	+28	1.48		2.78	+23	+10	2.98	3.22		
36	21	M.	Loss, 10. Recent gain, 5	12	0	+53	+35	+20	2.36		3.26	+20	− 6	2.62	3.13	− 6	3.09
37	34	F.	Loss, 35	24	0	+62	+29	+18	3.24		2.45	+ 6		1.68		+ 2	3.23
38	33	F.	Loss, 16	1	0	+49	+51		1.24	2.87							
39	62	F.	Loss, 48	12	0	+48	+25		2.11	1.91		+20			2.38		

CHART III

Hippuric Acid Excretion in Primary Hyperthyroidism
(Two stage operation)

No. cases	Average B.M.R. %						Average hippuric acid excretion in grams					
	On adm.	On 6th day	Postop. 1st stage	Preop. 2d stage	Postop. 2d stage	3 mos. check up	On adm.	On 6th day	Postop. 1st stage	Preop. 2d stage	Postop. 2d stage	3 mos. check up
39	+54	+36	+23	+21	+7	−7	1.88	2.33	2.27	2.51	2.66	*3.12
Percentage of normal hippuric acid determinations							2%	20%	7%	22%	44%	77%

* 2 recurrent cases and 1 case of myxedema not included in the determination.

the average hippuric acid excretion 2.51 grams. At this point 22 per cent of the cases had normal tests. Postoperatively the average hippuric acid excretion was 2.66 grams with 44 per cent of the cases having normal tests. At the three months check up in 16 cases the average basal metabolism was minus 7 per cent with the average hippuric acid excretion 3.12 grams. In calculating the average in this group of 16 cases, two cases of recurrent hyperthyroidism (4, 6) and one case of myxedema (2) were excluded. At this time 77 per cent of the cases had normal determinations. This average figure is affected by the presence of two cases (Nos. 14, 22) who had weights less than 100 pounds being 73 and 91 pounds respectively, and where the normal excretion would hardly be expected to be 3 grams.

In the 31 cases of adenomatous goiter with hyperthyroidism (table 3) the average basal metabolic rate on admission was plus 36 per cent and the average hippuric acid excretion 2.27 grams (chart 4). Seven cases, or 23 per cent, had normal hippuric acid excretion (Nos. 6, 8, 19, 22, 24, 29, 30). In this group of seven cases, five had not lost weight and two had taken iodine for long periods before admission. The average basal metabolic rate was plus 24 per cent and the average hippuric acid excretion 2.33 grams preoperatively. Eleven per cent of the cases had normal hippuric acid excretion at this point. Postoperatively, the hippuric acid excretion was 2.36 grams with 16 per cent of the cases being normal. At the three months' check up six cases had an average metabolic rate of minus 5 per cent with the hippuric acid excretion 3.34 grams.

A comparative study of these groups of cases (figure 1) shows that a close relationship exists between the level of the basal metabolism and the hippuric acid excretion. The cases with primary hyperthyroidism permitting a subtotal thyroidectomy had an average basal metabolism equal to the group of adenomatous goiters. The average admission hippuric acid excretion in the two groups was practically the same being 2.30 and 2.27 grams. The group of primary hyperthyroidism requiring the two stage operation had a higher average basal metabolism, plus 54 per cent, and a lower average hippuric acid excretion, 1.88 grams.

TABLE III

Hippuric Acid Excretion in Adenomatous Goiter with Hyperthyroidism
(One-stage operation)

Case	Age	Sex	Weight change, pounds	Duration of disease, years	Iodine prior to admission	Basal rate, per cent			Liver function, in grams			3 months check-up	
						On adm.	On 6th day	6th day postop.	On adm.	Preop.	Postop.	Basal rate	Hippuric acid
1	47	F.	Loss, 17	1.5	0	+33	+27	+13	2.30	2.95			
2	61	F.	Loss, 20	3	0	+44	+27	+32	2.11	2.01	2.13	− 3	3.10
3	53	F.	Loss, 12	0.33	0	+51	+28	+34	1.93	2.51		−10	2.56
4	33	F.	Loss, 10	0.5	0	+17	+14	+10	2.26	2.32	2.87		
5	30	F.	Loss, 30	3	0	+33	+15	+19	2.31	2.79			
6	54	F.	None	2	0	+38	+29	+52	3.60		3.47		
7	52	F.	Loss, 15 Regain, 5	2	0	+40	+28	+30	0.89	1.97	1.85	− 4	3.03
8	52	F.	None	0.25	0	+19		+ 7	3.45		3.56		
9	45	M.	Loss, 15	4.2	0	+70	+39	+23	2.89	2.99	1.42	− 8	3.69
10	60	F.	Loss, 10	2	2 mos.	+21	+11	+18	1.97	1.79	2.12		
11	66	F.	Loss, 20	6	0	+28	+10		0.54	Weight 79 pounds Postoperative death			
12	43	F.	Gain, 4	1	8 mos.	+63	+37	+25	2.33	2.71		−10	3.43
13	52	F.	None	2	0	+46	+32	+12	1.46	2.57			
14	57	F.	Loss, 15	1	4 mos.	+40	+38		2.11	1.79			
15	47	F.	Loss, 26	2	0	+60	+32	+23	2.44	1.05	2.84	− 8	4.26
16	57	M.	Loss, 70	6	0	+41	+24	− 4	1.11	1.30	1.58		
17	63	F.	Loss, 26	0.33	0	+50	+37	+26		2.45			
18	51	F.	None	2	0	+19	+14	+14	2.58				
19	57	F.	Loss, 40	0.33	0	+51	+35		3.49	3.77			
20	54	F.	Loss, 18	0.5	3 wks.	+18	+14		1.20				
21	40	F.	Loss, 13	1	0	+22	+ 5		0.92	1.58	1.64		
22	57	F.	Loss, 5	0.75	7 mos.	+26	+ 9		3.65				
23	49	F.	Loss, 28	0.66	3 mos.	+54	+44	+ 8	2.30				
24	37	F.	Gain, 5	3	0	+28	+ 9	+ 9	3.77				
25	41	F.	Loss, 20	2	0	+39	+22		2.14	2.48			
26	43	F.	Loss, 7	1	0	+12			1.81				
27	57	F.	Loss, 8	4	0	+38	+24		1.48				
28	52	F.	Gain, 4	2	0	+24			2.71	3.11	2.85		
29	62	F.	Loss, 40	3	5 mos.	+21	+16	+19	3.18		2.40		
30	47	F.	None	0.33	0	+50	+26		3.02				
31	61	F.	None	0.75	0	+19			2.18				

CHART IV

Hippuric Acid Excretion in Adenomatous Goiter with Hyperthyroidism
(One-stage operation)

No. Cases	Average B.M.R. %				Average Hippuric Acid Excretion in Grams			
	On Adm.	On 6th Day	Postop.	3 Mos. Check Up	On Adm.	Preop.	Postop.	3 Mos. Check Up
31	+36	+24	+20	−6	2.27	2.33	2.36	3.34
Percentage of normal hippuric acid determinations					23%	11%	16%	83%

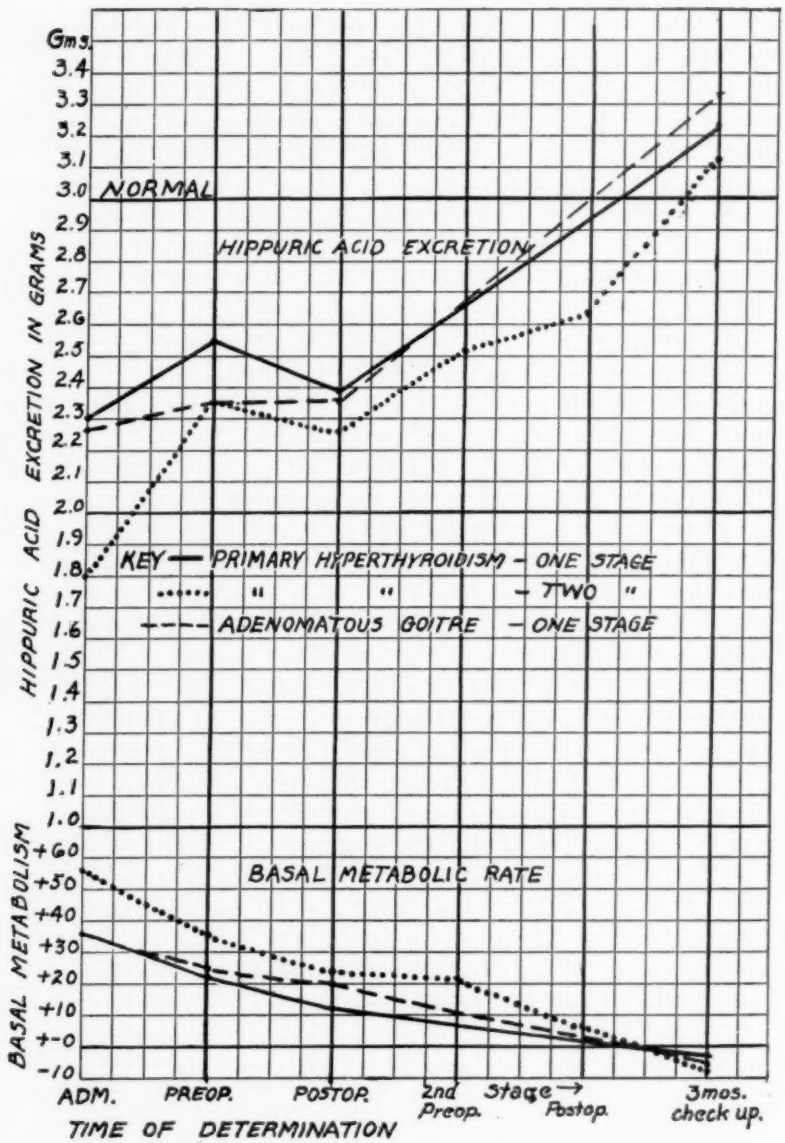

FIG. 1. Hippuric acid excretion and basal metabolism in hyperthyroidism.

As shown, the trend of the average hippuric acid during preoperative treatment in the cases of primary hyperthyroidism is upward. However, the group of adenomatous goiters have a fairly constant excretion. A slight postoperative drop occurred in the average hippuric excretion in the two groups of cases with primary hyperthyroidism. The hippuric acid excretion in the two stage cases showed a gradual increase at the time of the second operation with a continued rise postoperatively. All the groups then went to a normal average hippuric acid excretion at the time of the three months' check up. The trend of the average basal metabolic rate was downward in all the groups.

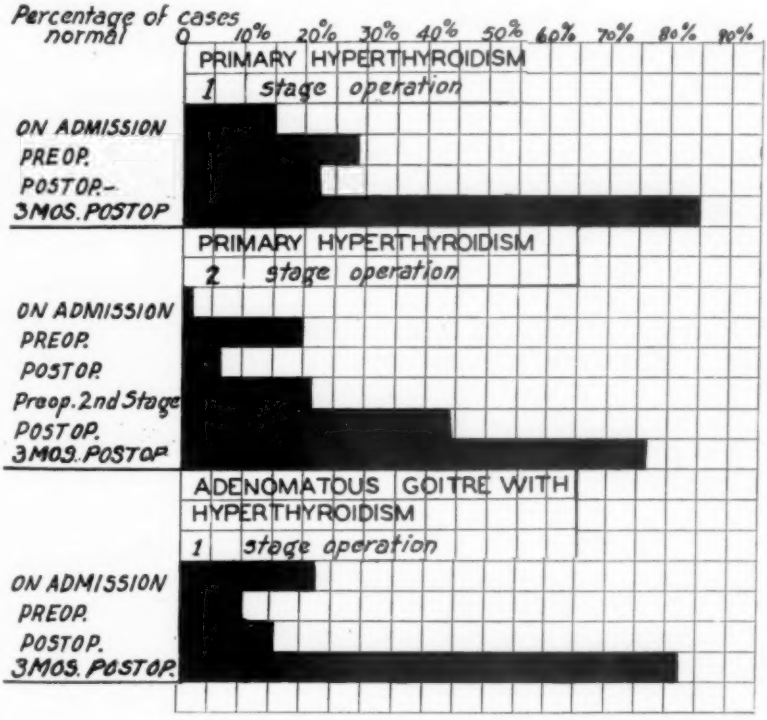

FIG. 2. Cases of hyperthyroidism with normal hippuric acid excretion.

When a comparison is made with the percentage of cases showing normal excretion in the three groups during the period of study certain features are worthy of mention. (Figure 2.) Only 2 per cent of the severe cases requiring a two stage operation had normal hippuric excretion on admission, as compared to 15 per cent in the group of lesser clinical severity having a subtotal thyroidectomy, and to 23 per cent in the group of adenomatous goiters. A rise in hippuric acid excretion occurred preoperatively in the groups of cases of primary hyperthyroidism but a slight drop appeared at

this stage in the adenomatous group. Postoperatively a drop occurred in the two stage group suggesting the effect of operative strain on the liver in these more toxic cases. A high per cent of normals occurred in all the groups at the time of the three months' check up.

It was found that the duration of the hyperthyroidism was not a potent factor in determining the degree of liver function reduction as shown in figure 3. Patients having acute hyperthyroidism were found to develop degrees of liver impairment in a few months where patients with milder types had little change even after years. This observation is corroborated by the fact that, whereas the average duration of the disease in the group of cases of primary hyperthyroidism having a subtotal thyroidectomy was

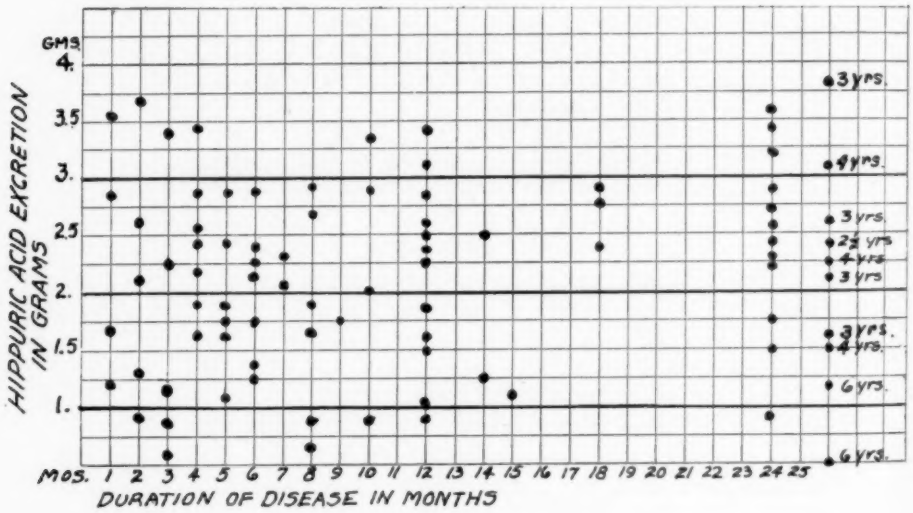

FIG. 3. Duration of *hyperthyroidism in relation to hippuric acid excretion.
* No iodine prior to admission.

10 months and in the group of adenomatous goiters 21 months, the hippuric acid excretion in both these groups was found to be the same.

In an attempt to relate the postoperative temperature and pulse response to the degree of functional impairment of the liver a comparison was made of the postoperative clinical course and the level of the hippuric acid excretion. A series of cases was selected at random having hippuric acid excretion of varying amounts; below one gram; between 1 and 2 grams; between 2 and 3 grams; and over 3 grams. (Figures 4, 5, 6, 7, 8.) No apparent uniformity was found to occur in the postoperative temperature and pulse response in the various hippuric acid levels. A typical crisis reaction did occur in a case having a hippuric acid excretion below 1 gram, but severe reactions occurred in cases having excretions even above the

normal of 3 grams. One case is of particular interest (figure 6) in that with the same level of the hippuric acid excretion prior to the first and second operation she had a normal response after the first operation and suffered a severe reaction after the second. Thus it is shown that the type

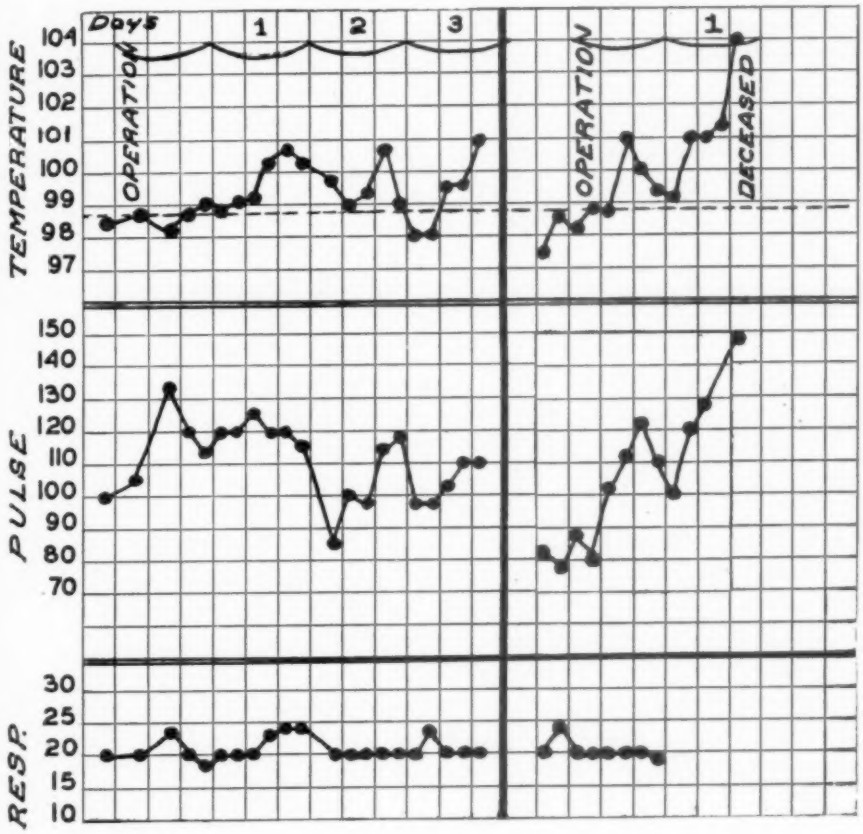

FIG. 4. Postoperative clinical response—hippuric acid excretion less than 1 gram.

Mrs. M. O. Age 50.
Adm. B.M.R. + 69.
Dur. 6 months.
Wt. loss—14 lbs.
Rt. Hemithyroidectomy.
Hippuric Acid Excretion } .84 gram / .43 gram

Mrs. A. J. Age 66.
B.M.R + 28.
Dur. 6 years.
Wt. loss—20 lbs.
Rt. Hemithyroidectomy.
Hippuric Acid Excretion } .54 gram / .67 gram

of postoperative response cannot be predicted from the level of the hippuric acid excretion. This tends to cast a shadow of doubt on the opinion that the thyroid crisis reaction is entirely on the basis of the liver function impairment.

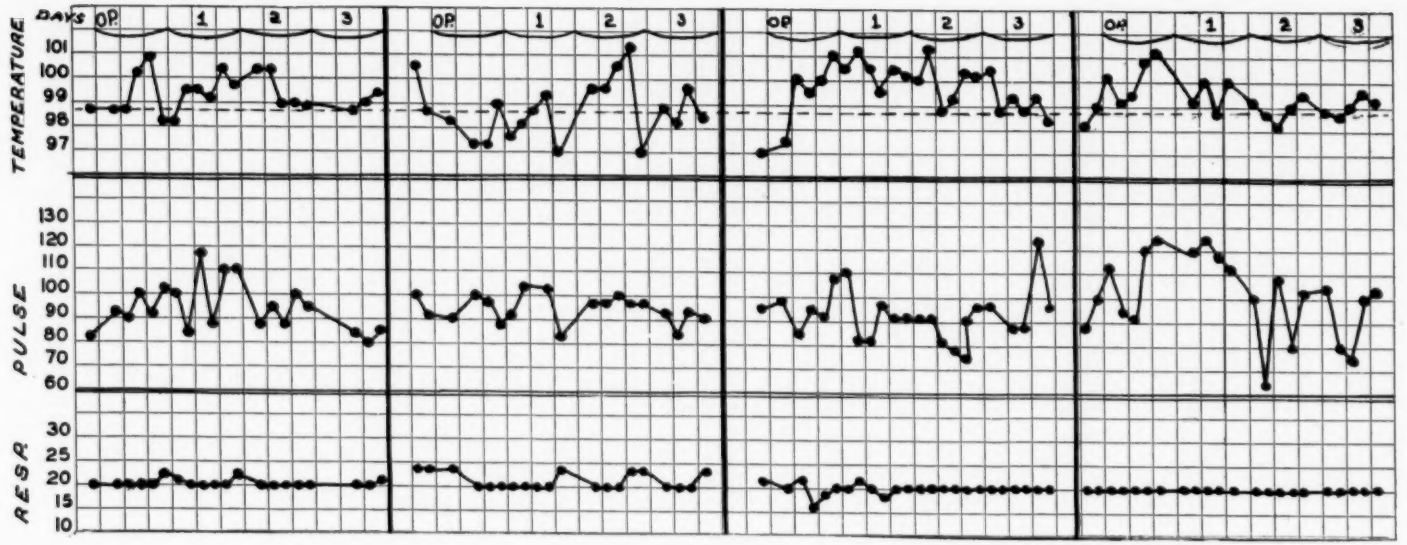

FIG. 5. Postoperative clinical response—hippuric acid excretion between 1 and 2 grams.

Mrs. R. H. Age 40.
B.M.R. + 22.
Dur. 1 year.
Wt. loss—13 lbs.
Subtotal Thyroidectomy.
Liver Function: .92 Gm. / 1.58 Gm. / 1.64 Gm.

Mr. M. K. Age 57.
B.M.R. + 41.
Dur. 6 years.
Wt. loss—70 lbs.
Subtotal Thyroidectomy.
Liver Function: 1.10 Gm. / 1.30 Gm. / 1.58 Gm.

Mrs. J. L. Age 52.
B.M.R. + 30.
Dur. 2 months. Recurrent.
Wt. loss—None.
Removal of Remnants
Liver Function: .98 Gm. / 1.22 Gm. / 1.10 Gm.

Mrs. M. M. Age 36.
B.M.R. + 32.
Dur. 1 month.
Wt. loss—29 lbs.
Subtotal Thyroidectomy.
Liver Function: 1.70 Gm. / 1.62 Gm.

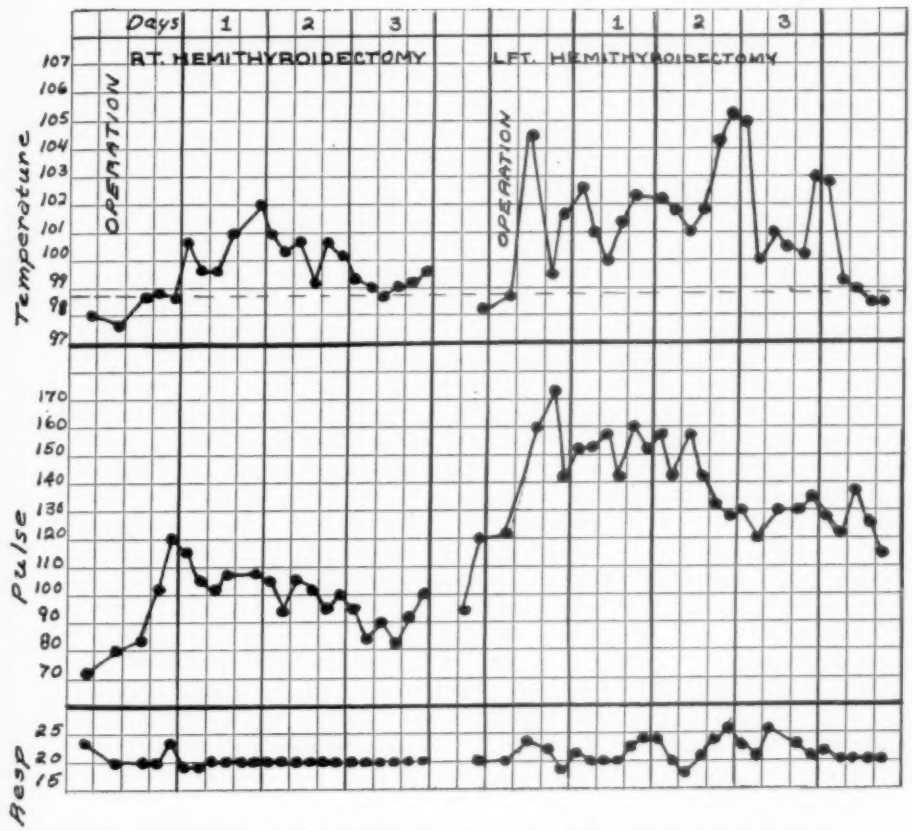

FIG. 6. Postoperative clinical response—hippuric acid between 2 and 3 grams.

Miss A. L. Age 24.
B.M.R. 1st Stage + 76. 2d Stage + 44.
Duration 7 Mos.
Wt. loss—20 lbs.

	1st Adm.	2d Adm.
Liver Function	2.03 Gm.	2.38 Gm.
	2.24 Gm.	

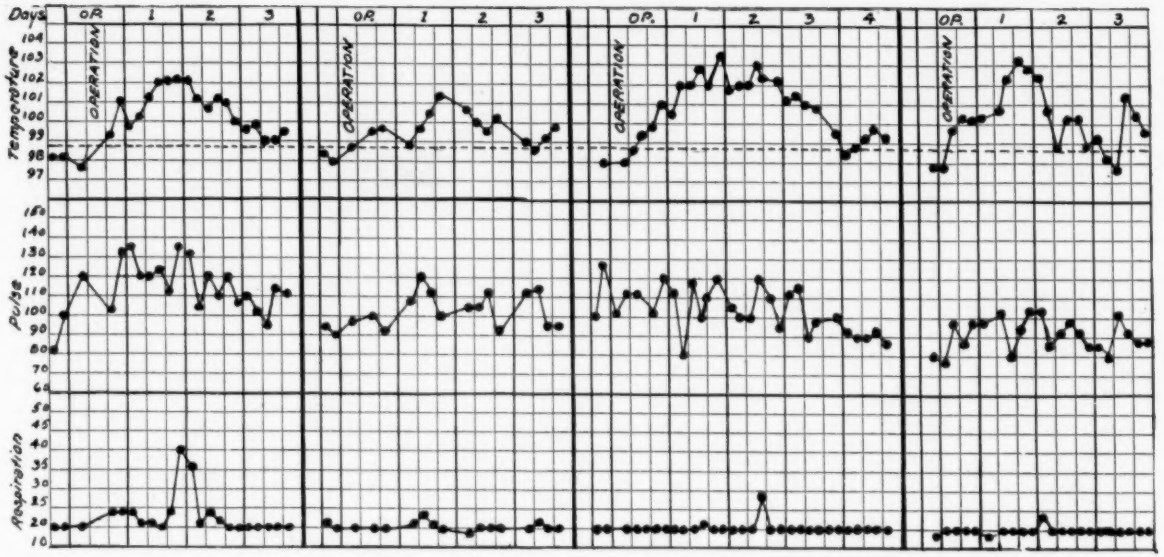

FIG. 7. Postoperative clinical response—hippuric acid excretion between 2 and 3 grams.

Mrs. G. H. Age 23.
B.M.R. + 29.
Dur. 6 months.
Wt. loss—None.
8 lbs. Gain.
Subtotal Thyroidectomy.
Liver Function } 2.96 Gm. 2.83 Gm.

B.M.R. + 37.
Dur. 7 months.
Weight—Gaining.
Subtotal Thyroidectomy.
Liver Function } 2.28 Gm. 2.20 Gm.

Miss L. B. Age 30.
Miss A. E. Age 30.
B.M.R. + 49.
Dur. 2 months.
Wt. loss—20 lbs.
Subtotal Thyroidectomy.
Liver Function } 2.16 Gm. 2.84 Gm.

Mr. J. K. Age 48.
B.M.R. + 51.
Dur. 1 year.
Wt. loss—26 lbs.
Subtotal Thyroidectomy.
Liver Function } 2.83 Gm. 3.05 Gm.

Liver Function } 2.28 Gm. / 2.20 Gm.

Subtotal Thyroidectomy.
Liver Function } 2.83 Gm. / 3.05 Gm.

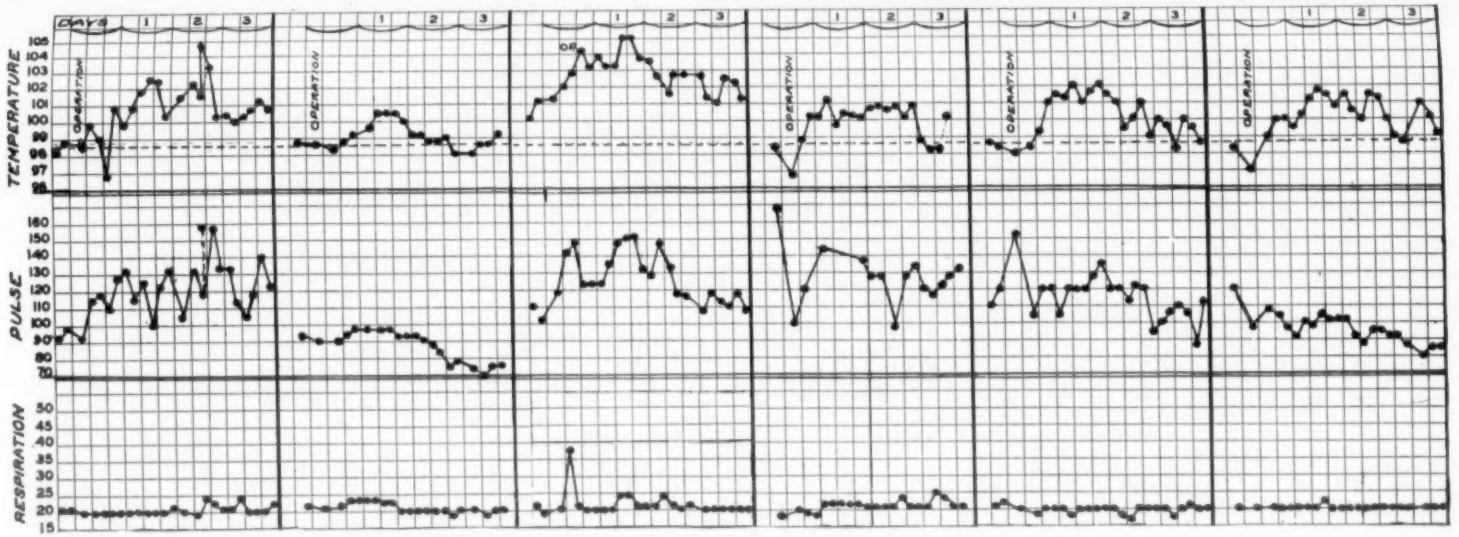

FIG. 8. Postoperative clinical response—hippuric acid excretion over 3 grams.

Mrs. R. N. Age 29.
B.M.R. + 30.
Dur. 9 months.
Gaining weight.
Subtotal Thyroidectomy.
Liver Function } 3.43 Gm. / 3.00 Gm.

Mrs. I. L. Age 39.
B.M.R. + 45.
Dur. 1 month.
Wt. loss—None.
Subtotal Thyroidectomy.
Liver Function } 3.79 Gm.

Mr. R. M. Age 32.
B.M.R. + 73.
Dur. 6 months.
Wt. loss—50 lbs.
Rt. Hemithyroidectomy.
Liver Function } 3.33 Gm. / 3.78 Gm.

Mr. R. C. Age 36.
B.M.R. + 40.
Dur. 1 year.
Wt. loss—25 lbs.
Bilateral Pole Ligation.
Liver Function } 3.14 Gm. / 3.43 Gm.

Hippuric Acid Excretion, Blood Cholesterol and Serum Protein

Hurxthal,[27] Adler [28] and others have reported that the blood cholesterol is reduced in hyperthyroidism. A return toward normal occurs after preoperative treatment and especially after thyroidectomy. Epstein and Greenspan [29] more recently have attributed the cholesterol reduction to parenchymatous liver change. It is therefore to be assumed that in hyperthyroidism the lowering of the blood cholesterol is related to liver impairment. It has also been accepted that in diseases of the liver a lowering occurs in the serum protein of the blood with an alteration of the albumin globulin ratio. A comparative study of the hippuric acid excretion, blood cholesterol, and serum protein was carried out in 19 cases (table 4). In

Table IV

Blood Cholesterol in Hyperthyroidism*
Hippuric acid excretion and serum protein

Case	Hippuric acid in grams		Blood cholesterol, mg.		Serum protein, gm.	
	Admission	Preoperative	Admission	Preoperative	Admission	Preoperative
1	2.16	2.84	127	176	6.3	6.0
2	2.22	1.93	154	188	7.6	6.6
3	0.92	1.37	97	170	6.0	6.5
4	2.83	2.94	138	186	6.8	6.6
5	2.62	3.20	136	161	6.1	7.3
6	1.07	2.32	232	220	6.4	7.6
7	2.31	2.79	121	161	6.4	6.1
8	2.36	2.96	173	137	7.3	8.2
9	2.45	2.88	140	171	6.3	6.6
10	1.35	1.72	104	142	5.3	5.4
11	2.64	3.04	109	169	7.2	6.9
12†	2.30	2.95	158	196	6.0	8.8
13	2.55	2.91	165	177	6.7	7.2
14†	2.11	2.01	161	192	6.4	6.8
15	1.65	2.60	176	190	6.3	4.9
16	2.03	2.24	133	182	6.4	5.9
17†	1.93	2.51	150	225	6.5	6.9
18	1.98	1.26	183	232	6.8	6.4
19†	2.31	2.79	201	203	6.7	6.7
Average	2.06	2.48 (20%)	150	183 (20%)	6.5	6.7
Increase		0.16		17		1.0
Decrease		0.3		2		0.9

* No iodine prior to admission.
† Cases having adenomatous goiter with hyperthyroidism; all the others primary hyperthyroidism.

this group of cases the average admission hippuric acid excretion was 2.06 grams, cholesterol 150 mg., and serum protein 6.5 gm. (chart 5). Preoperatively the hippuric acid excretion and the blood cholesterol showed increases of 20 per cent. In 16 cases the hippuric acid excretion increased and in 17 cases the blood cholesterol increased. An apparent relationship was found to exist between the level of the hippuric acid and the blood

CHART V

Cholesterol Study of Hippuric Acid Excretion—Blood Cholesterol and Total Serum Protein

No. Cases	Average Hippuric Acid in Grams		Average Blood Cholesterol in Mg.		Average Total Serum Protein in gm.	
	On Adm.	Preop.	On Adm.	Preop.	On Adm.	Preop.
19	2.06	2.48	150	183	6.5	6.7
Percentage increase		20%		20%		

cholesterol. However, no relationship was found to exist between the level of the hippuric acid and the level of the total serum protein (figure 9). The average total protein on admission was found to be 6.5 gm. Preoperatively the determination was practically the same, being 6.7 gm. Macrocytic anemia due to liver disease did not occur in the cases studied.

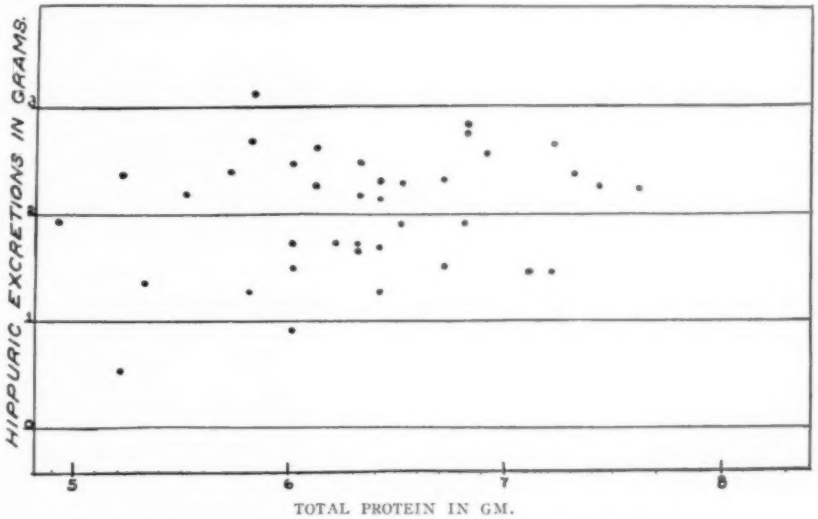

FIG. 9. Hippuric acid excretion and total serum protein.

Mr. H. E. Age 40.
B.M.R. + 56.
Dur. 2 years.
Wt. loss—50 lbs.
Subtotal Thyroidectomy.
Liver Function } 3.48 Gm. 3.55 Gm. 3.52 Gm.

Mr. W. H. Age 32.
B.M.R. + 42.
Dur. 1 year.
Wt. loss—30 lbs. Regained 8.
Subtotal Thyroidectomy.
Liver Function } 3.43 Gm. 3.84 Gm.

APPARENT EFFECT OF DIGITALIS ON HIPPURIC ACID EXCRETION

In the course of the study certain cases were found to have hippuric acid excretions which were exceptionally low for the degree of severity of

their thyroid disease. Others showed substantial drops in the hippuric acid excretion following preoperative treatment. In seeking an explanation for these occurrences it was found that these cases had received digitalis prior to admission or during the course of preoperative treatment. Cardiac complications such as pulse irregularities and myocardial failure had indicated the use of the medication. One case after seven days of digitalis had a drop in the hippuric acid excretion from 1.77 grams to 0.57 gram; one case after 26 days of digitalis had a drop from 1.09 grams to 0.54 gram; one case after 7 days of digitalis had a drop from 1.33 grams to 0.88 gram. Another case demonstrated this drop on two occasions, the first time from 3.10 grams to 0.77 gram after seven days of digitalis and again from 2.80 grams to 1.46 grams after 10 days of digitalis. These observations suggest that in hyperthyroidism digitalis is toxic to the liver.

Attempts at Altering the Hippuric Acid Excretion

Having shown that the function of the liver is reduced in hyperthyroidism attempts at enhancing the return to normal preoperatively were instituted. A number of methods were tried, each one having a suggestive clinical reason for its employment.

As a high carbohydrate-low fat diet is the accepted treatment for liver disease 17 cases were placed on this regime. The usual hospital diet for patients with hyperthyroidism is high in calories and vitamins with an average content made up of carbohydrate 377 grams, protein 119 grams, and fat 200 grams, with a caloric value of 3784 calories. The diet employed had individual variations ranging in carbohydrate from 395 grams to 1099 grams and in fat from 22 grams to 60 grams, with a caloric value from 2700 to 5000 calories. The protein remained between 60 to 80 grams. The average hippuric acid excretion for the group on admission was 1.77 grams and after approximately 10 days on the diet 2.40 grams with 13 cases showing striking increases in the hippuric acid. Although normal determinations were not obtained after such a forced carbohydrate feeding it seems logical to suppose that this is the most suitable diet for patients with this disease.

Glycine given in 15 grams daily doses returned the hippuric acid excretion to normal in three cases. One of these cases had on admission a hippuric acid excretion of 0.92 gram. The effect of glycine on the hippuric acid excretion has been reported by Quick. The placing of readily available glycine in the system by such large doses suggests a possible source of error for the test as the liver may not be entirely involved in the conjugation of the benzoic acid to hippuric acid; other factors may play a part.

Conclusions

1. Reduction in the liver function as shown by the hippuric acid excretion test was observed in a high proportion of cases of hyperthyroidism.

On admission only 18 cases out of 148 cases had a normal response to the test.

2. The degree of change in liver function is in direct relation to the severity of the hyperthyroidism, as determined by the basal metabolic rate and the clinical opinion as to the necessity for a one or a two stage operation.

3. No apparent correlation was found to exist between the liver function and the duration of the hyperthyroidism. The absence of weight loss or a history of previous iodine administration was usually noted in conjunction with a normal admission liver function test.

4. Improvement in liver function occurred during preoperative treatment in the cases with primary hyperthyroidism. No apparent change was noted in adenomatous goiter with hyperthyroidism.

5. Normal liver function was found in a high per cent of cases three months postoperative, indicating that the liver damage from hyperthyroidism is rarely permanent.

6. No apparent relationship was demonstrated between the level of the liver function and the degree of postoperative pulse and temperature response.

7. A close relationship was found to exist between the blood cholesterol and the hippuric acid excretion.

8. The use of a high carbohydrate diet apparently improved the liver function as indicated by increased hippuric acid excretion.

9. As the liver plays a vital rôle in the general body metabolism the change which occurs in its function in hyperthyroidism must represent a serious physiological handicap to the patient.

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GONORRHEAL ENDOCARDITIS; A REPORT OF THREE CASES, ONE TREATED WITH FEVER THERAPY *

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THERE have been numerous reports of the treatment of gonorrheal infections with fever therapy during the past few years. These reports have dealt mainly with cases of gonorrheal arthritis, though gonorrheal pelvic inflammatory disease and other local manifestations of the infection also have been treated successfully by heat therapy. We wish to report a case of gonorrheal endocarditis treated by fever therapy unsuccessfully, and also to report two cases of gonorrheal endocarditis not previously reported. Freund and Anderson reported the recovery of a case of gonorrheal endocarditis treated by hyperpyrexia at the First International Conference on Fever Therapy in March 1937. Williams [1] reports a case of proved and one of probable gonorrheal endocarditis treated with artificial fever in the Kettering hypertherm. In the proved case fever treatment resulted in sterilization of the blood stream and, as established at necropsy, sterilization of the endocardial vegetations. Death, Williams attributed to a co-existing syphilitic cirrhosis of the liver and uremia. In the case designated as probable gonorrheal endocarditis, fever treatment resulted in prompt recovery. Krusen and Elkins [1a] have also reported a case of gonococcemia with endocarditis treated with fever therapy without effect.

While Wagner-Jauregg originated true fever therapy in 1918 for dementia paralytica, it was not until the work of Carpenter, Boak, Mucci and Warren [2] in 1933, that fever therapy for gonorrheal infections was placed on a rational basis. These workers investigated the thermal death time of 15 strains of gonococci at 39°, 40°, 41°, 41.5° and 42° C. in vitro. Seven of these strains were isolated in 1920, one in 1922 and the remaining seven were isolated one to four months previously. In all instances the "recently" isolated strains, with the exception of one "old" strain, showed the least resistance to 41°, 41.5° and 42° C. At 41.5° C. and 42° C. 99 per cent of the organisms were rendered non viable in two hours. At 41.5° C. from seven to twenty hours and at 42° C. five to fifteen hours were required for sterilization. They felt that the in vitro thermal death time was short enough at these temperatures to suggest fever therapy as a valuable therapeutic aid. They thought that complete sterilization could not be obtained with only one session of fever of five hours. Their work suggested that in vivo something other than the mere heating occurred to make the organisms

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more susceptible to destruction by the body. In 1936 Thompson, Sheard and Larson[3] tested a number of organisms at 107° F. for as long as 24 hours to determine the effect at temperatures which the human body could stand. Of the organisms tested only the gonococcus showed complete sterilization, and this was true with as short a period as six hours.

Desjardins, Stuhler and Popp[4] reported a series of 76 cases of gonorrheal infection, 36 with urethritis and 40 with complications, treated by fever therapy. They reported 89.5 per cent cured, and 9.2 per cent improved. The average number of sessions was six periods of six to eight hours per patient. They point out that advanced age with cardiovascular changes and organic heart disease at any age are severe handicaps to fever therapy. Functional heart disease may or may not interfere with satisfactory treatment. They feel that severe disturbance of renal function may make fever therapy difficult or contraindicated but will interfere less than cardiac or cardiovascular lesions. Diabetes under satisfactory control is no contraindication to treatment. Pulmonary tuberculosis itself is not a contra-indication, but the impairment of respiratory function may make it impossible to maintain safely a satisfactory temperature level. They report an increasing pulse rate at the beginning of the treatment through the phase of rising temperature and then stabilization at 120 or, more especially in unstable patients, 140 to 150 with large amplitude of oscillations. If the pulse exceeds 160, the fever is terminated at once and a new trial made two or three days later. If the pulse again rises too high, attempts at fever therapy are discontinued. They observed an almost constant rise of the blood pressure more rapidly than that of the temperature. After the maximum temperature has been reached, the systolic pressure slowly falls so that by the end of the session it is below the original level. The diastolic pressure falls slowly, 10 to 35 mm. The most important point is the careful observation of the pulse pressure, and if it is reduced to 20 mm. or less, the session should be terminated at once.

The use of fever therapy in endocarditis is not a new therapeutic procedure. Fulton and Levine[5] report two cases of subacute bacterial endocarditis treated with rat-bite fever; another in which malarial inoculation was employed though no chills and fever resulted; a Bier operation was performed on another; two cases were given typhoid vaccine intravenously, in one of which a temporary disappearance of the fever occurred; four patients were given subcutaneous injections of turpentine to produce sterile abscesses. In one of these cases the temperature fell to normal and remained so for more than a month. None of these procedures, however, were of permanent benefit in any case.

Thayer[6, 7] pointed out that gonorrhea is an infection, focal at first, which spreads both by local extension and by the blood stream. A general septicemia then develops with a variety of metastases, i.e., arthritis, synovitis, myositis, and not infrequently endo-, myo- or peri-carditis. He reported 23 cases of gonorrheal endocarditis, 11.6 per cent of the cases of acute endo-

carditis at the Johns Hopkins Hospital. Sixteen of his cases were males and 11 of the total cases were white. The age varied from 9 to 42 years. Evidence of preëxisting valve damage was present in only 5 of the 23 cases thus proving the observations of many clinicians of the frequency of involvement of previously undamaged valves. Most cases followed urethritis. Four cases followed puerperal complications. The time of onset of the septicemia varied. In one case the onset was almost coincident with the urethritis, in four cases within two weeks, two within a month and the remainder of uncertain time.

In seven of his cases a history of arthritis in the course of the illness was obtained. Thayer felt this was an unusually low incidence and in 54 cases he collected from the literature 68.5 per cent had arthritis.

The symptoms are those of a septicemia. The onset sometimes is gradual with headache, lassitude, sweating, vague muscle pains, or more sudden with a sharp chill as occurred in our case. The majority of cases have chills and severe sweats. Hamman and Wainwright [8] point out in a study of the diagnosis of obscure fever that these symptoms are those of the classical form but that the disease may cause a relatively benign, long continued infection with a low fever, slight or absent leukocytosis and with involvement by preference of the aortic valves. The diagnosis is often overlooked since the gonococcus is difficult to culture. Hamman and Wainwright [8] report 90 cases of obscure fever of which two cases were gonorrheal endocarditis and one of these was diagnosed only at autopsy. Emboli are common. Jaundice has been reported in patients with gonorrheal infections. Popper and Weidman [9] have written an interesting report on "Gonotoxic icterus." They believe that hepatic impairment results from gonotoxins and a picture simulating catarrhal jaundice is produced. Petechiae or other skin eruptions are frequent. Bakst, Foley and Lamb [10] report a case of gonococcemia with erythema nodosum and have collected 18 cases from the literature with skin manifestations. These skin lesions were maculopapular, pustular, macular, purpuric and urticarial. The spleen was palpable in 21 per cent of Thayer's cases. Clubbing of the fingers was noted in none of Thayer's cases. The blood shows a rapidly developing anemia and a high leukocytosis, over 30,000 in 42 per cent of Thayer's cases. The gonorrheal complement fixation is positive in a high percentage of cases and is of considerable assistance in diagnosis. Blood culture showed gonococci in 10 of Thayer's cases before death and in 13 of his cases gonococci were isolated from the heart's blood or the vegetations at autopsy. In one case the organism was isolated from the kidney. The difficulty in obtaining a positive blood culture is one of the characteristics of this disease.

Dieulafoy [11] reported a case in which both gonococci and pneumococci were found in the sputum. Two of Thayer's cases had pleurisy and in one of these the gonococcus was cultured from the fibrinopurulent fluid. The urine examination showed albuminuria, casts, leukocytes, epithelial cells and erythrocytes. These signs are more marked in cases of long duration. The

majority of Thayer's cases had acute or subacute nephritis, four showing anasarca and hydrops.

Thayer's study of the pathology of these cases shows the frequency of involvement of the aortic valve and the relative frequency of pulmonic valve involvement. In his series the aortic valve was involved in 66 per cent, mitral valve 19 per cent, pulmonic valve 23.8 per cent, and tricuspid valve in 23.8 per cent. The process is notably ulcerative and with exuberant vegetations, pink or gray, irregularly lobulated, soft and friable. Mural endocarditis was present in 61.9 per cent of his cases and especially notable was involvement of the aorta. In two cases mural involvement of the aorta was the only lesion. Pericarditis was present in 28.5 per cent of the cases.

The prognosis of gonorrheal endocarditis is not necessarily fatal. Solomon, Hurwitz, Woodall and Lamb [12] found 148 cases of gonorrheal endocarditis reported in the literature of which 10 survived despite the presence of cardiac involvement, a mortality rate of 93 per cent. A review of the literature by Bakst, Foley and Lamb [10] revealed 27 cases of gonococcemia without demonstrable endocarditis with recovery.

The treatment of this condition is discouraging. Gonococcus vaccine has been given by many, and some of the recovered cases received vaccine. However, one of the cases reported here received vaccine with no benefit. Perry [13, 14] reports a case of unquestioned gonorrheal endocarditis treated by frequent small blood transfusions with recovery. Vaccines were tried in his case, but the reactions were so severe that this form of treatment had to be discontinued. Wheeler and Cornell [15] report a case with intermittent bacteremia from a pelvic focus treated by radical extirpation with recovery. Garlock [16] reports a case with a positive blood culture, diagnosed gonorrheal endocarditis, in which he performed a salpingohysterectomy. The temperature fell to normal, blood culture became negative, and the patient was discharged after seven weeks. Six months later there was no demonstrable lesion in the heart. Newman [17] reports a case with recovery in which the critical drop in temperature occurred following a febrile episode during which the temperature was the highest that it had been at any time during the illness. Newman commented on this fact as of some importance in the ultimate recovery. However, other cases reported have had temperatures as high or higher without so favorable an outcome.

Dees and Colston [18] report on the use of sulphanilamide in gonococcal infections. This suggests the use of this drug in the endocardial form of this disease. We hope there will be reports in the literature bearing on this phase in the near future.

Case Reports

Case 1. A 48-year-old Jewish business man was first seen June 30, 1936 complaining of chills, fever and severe sweating of one week duration. On April 13, 1936 he had had an acute gonorrheal urethritis treated by local injections. On June 8, 1936 he had a left epididymitis treated by bed rest and applications of ice. On

June 21 he had a chill followed by a feeling of fever and sweating. The following day he noted a punctate skin rash on the left leg, hands and left arm.

The patient's family and social histories were essentially irrelevant except for sexual irregularities. The past history was irrelevant except for gonorrhea in 1927. Physical examination at his home on June 30 revealed a well developed and nourished white male not appearing acutely ill. The head and neck were entirely normal. There was no cervical, axillary or inguinal adenopathy. The thorax was symmetrical and expanded equally and well. The apex impulse was visible 8 cm. from the mid-sternal line in the fifth interspace; the right heart border was at the right sternal margin. No palpable thrills were felt. Heart tones were normal and no murmurs were heard. A_2 was greater than P_2. Blood pressure was recorded at 120 mm. of Hg systolic and 75 mm. diastolic. The radial pulses were equal and regular at a rate of 88.

The lung fields were normal to percussion and auscultation. Examination of the abdomen was normal. The liver, spleen and kidneys were not palpable. Examination of the genitalia revealed a small amount of clear mucous discharge from the urethra which did not show gram negative intracellular diplococci. The right testicle was not completely descended and was palpable just above the pubis. The left testicle was somewhat enlarged, and the epididymis was nodular, thickened and moderately tender. Rectal examination revealed a somewhat nodular, non-tender prostate of normal size. On the left lower leg, both hands, and on the left arm were 15 or 20 dull red lesions 2 to 3 mm. in diameter. They were considered questionable petechiae. The deep tendon reflexes were equal and active in both upper and lower extremities.

Urine examination showed a specific gravity of 1.013; acid reaction; albumin, slightest possible trace; sugar negative; the sediment showed 20 to 25 white blood cells per high power field, rare finely granular casts and no red blood cells. Hemoglobin 82 per cent (Newcomber); red blood cells 4,570,000; white blood cells 14,500. Examination of a blood smear revealed no malarial parasites. Differential blood count: Polymorphonuclears 77 per cent, lymphocytes 10 per cent, monocytes 5 per cent, eosinophiles 1 per cent, band forms 5 per cent, young lymphocytes 2 per cent. Agglutination tests for typhoid, paratyphoid a and b and undulant fever were negative. Complement fixation for gonorrhea was positive.

During the following week the patient's temperature was as high as 102° (F.) on two evenings and these rises were followed by drenching sweats. Roentgen-ray examination of the chest on July 6, 1936 showed no evidence of pulmonary disease or cardiac enlargement. July 7, 1936 he was admitted to the Peter Bent Brigham Hospital with a diagnosis of suspected gonorrheal bacteremia. The history and physical examination were essentially as given above. Urine examinations showed a specific gravity from 1.005 to 1.007; no albumin or sugar. The sediment showed 25 to 50 white blood cells on one occasion and 3 to 5 thereafter. Hemoglobin 95 per cent (Sahli), red blood cells 4,680,000; white blood cells 9,500. Differential blood count essentially as before. Blood Hinton negative. Phenolsulphonephthalein test showed 40 per cent excretion in two hours and 10 minutes.

A blood culture taken July 8, 1936 showed a gram negative diplococcus. The blood was drawn into dextrose broth and cultured under partially anaerobic conditions for four days. Transfers were then made to a chocolate agar slant and a few small colonies grew out under partial anaerobiasis, but no growth occurred under aerobic conditions. On blood agar slants there was moderate growth under partial anaerobiosis after several days but no growth under either completely aerobic or anaerobic conditions. There was no acid or gas formation in cultures with dextrose, maltose, lactose, xylose or mannite even after the addition of fresh normal blood. In dextrose broth under aerobic conditions at 37° C. there were a few gram negative diplococci on a loop smear after 10 days. Anaerobically at 37° C. there was no growth in

dextrose broth nor was there growth under any condition at room temperature. In an approximate 1:2 dilution with antimeningococcic serum there was no agglutination. Culture taken on July 9 showed a similar organism but a culture taken on July 13 showed no growth after eight days. During the week in the hospital his temperature ranged from 101.8° F. to 97° F. The pulse ranged from 98 to 68. Respirations averaged 20 per minute. At the patient's request he was discharged to his home, July 14, 1936. At no time during the hospital stay was there any change in the physical findings. The heart showed no murmurs. The blood pressure was consistently 110 to 120 mm. Hg systolic and 75 to 80 mg. Hg diastolic.

During the following week he continued to have a daily rise in temperature with several severe chills. A soft basal systolic murmur was heard July 19. He was advised to return to the hospital for fever therapy.

He was readmitted to the Peter Bent Brigham Hospital July 21, 1936 and received his first treatment July 22, 1936. Fever therapy was given with diathermy, the temperature being elevated to 105.6° to 106.6° F. (rectal) for three hours. During the treatment the pulse varied from 132 to 138 and was of good quality.

On July 24 (103 days after the onset) a blowing diastolic murmur was heard along the left sternal border loudest in the third interspace. The blood pressure was 108 mm. Hg systolic and 60 mm. Hg diastolic. There did not appear to be any change in symptoms though he had complained of some sense of pressure over his chest after the first treatment.

July 24. Second fever therapy treatment. The temperature was raised to 106.2° F. (rectal) in the diathermy machine and prolonged 3½ hours. The patient's pulse varied from 134 to 140 during the treatment. After the treatment he appeared to be in relatively good condition. July 25, blood pressure 108 mm. Hg systolic and 52 mm. Hg diastolic. The diastolic murmur was louder than before. There was also a soft apical systolic murmur. The blood pressure was 108 mm. Hg systolic and 52 mm. Hg diastolic.

July 27. Third fever therapy treatment. Temperature maintained at 106° F. (rectal) for two hours 10 minutes. Patient then complained of feeling weak and the treatment was stopped. July 28. There was a loud blowing diastolic murmur now audible at the base and along the left sternal border. The systolic murmur had also become more harsh and loud. Blood pressure was 110 mm. Hg systolic and 58 mm. Hg diastolic. The lung fields were clear to percussion and auscultation. The liver edge was palpable 2 cm. below the right costal margin and moderately tender. The spleen was not palpable. The left epididymis was somewhat more tender than before. The prostate was not enlarged or tender. There was no peripheral edema and no petechiae or clubbing of the fingers.

July 20. Fourth fever therapy treatment. Rectal temperature maintained at 106° to 106.4° F. for 4½ hours. Pulse 116 to 124 during treatment. Blood pressure 108 mm. Hg systolic and 48 diastolic.

July 31. Hemoglobin 76 per cent; red blood cells 4,160,000; white blood cells 13,000. Differential count: Polymorphonuclears 90 per cent; lymphocytes 5 per cent; eosinophiles 2 per cent; monocytes 3 per cent.

August 2. Fifth fever therapy treatment. Temperature raised to 106° to 106.4° F. for 4½ hours. August 6. The patient was obviously failing. Transfusion of 400 c.c. of citrated blood was followed by a severe reaction. Both the diastolic and systolic murmurs became much louder. The liver was palpable 2 cm. below the right costal margin. The respirations were 40 to 50 and the pulse 100 to 120. He had frequent attacks of weakness with increased dyspnea. He gradually became weaker and died August 13.

Clinical Diagnosis: Gonococcal sepsis; gonorrheal endocarditis with involvement of the aortic valve. Left epididymitis. Bilateral hydrothorax. Pulmonary edema.

Postmortem Examination. No free fluid in the peritoneal cavity. The liver extended 4 cm. below the right costal margin. The spleen was markedly enlarged with a few adhesions over the surface. On section there were areas of infarction.

The right pleural cavity contained 450 c.c. and the left 750 c.c. of cloudy fluid. The pericardial cavity contained 60 c.c. of straw-colored fluid and showed smooth moist surfaces.

The heart weighed 470 grams before fixation and 395 grams after fixation. Valve measurements: Tricuspid valve 10 cm.; pulmonary valve 6 cm.; aortic valve 6.5 cm.; mitral valve 8 cm. The aortic valve was the site of an acute ulcerative endocarditis. The left posterior cusp of the aortic valve was nearly split into two portions by a granular, productive lesion which rose slightly above the normal height of the free edge of the leaflet. The lesion also penetrated the wall of the adjacent anterior cusp extending directly through it in continuity at the attachment of the cusp. It then produced a rather flat papillomatous projection on the inner aspect of the lateral margin of the anterior cusp. (Figure 1.) The free margin of the anterior cusp was freely moveable, translucent but fixed by the penetrating growth at the junction with the left posterior cusp. The right posterior cusp was free from involvement. The openings to the coronary vessels were not encroached upon by the lesion. There was slight bulging of the *annulus fibrosus* of the pulmonary valves from the ulcerative action of the lesion in penetrating from the left posterior to the anterior cusp of the aortic valve. The tricuspid, pulmonary and mitral valves were not involved in the ulcerative process. The myocardium was of a uniform reddish brown color and free from evidence of infarction. The papillary muscles and chordae tendineae of both mitral and tricuspid valves appeared normal.

Microscopic sections showed Aschoff bodies in the myocardium. Sections from the vegetations on the aortic valve showed a mass of necrotic debris surrounded at its base by a few polymorphonuclear leukocytes. There were some colonies of bacteria in the necrotic material and some scattered bacteria were also seen. In the eosin-methylene blue and Giemsa stained sections were found small biscuit shaped diplococci, many of which were intracellular. These were decolorized in the sections stained by Gram's method and hence were gram negative.

The lungs showed a diffuse bronchopneumonia.

The gastrointestinal tract and pancreas were essentially normal. The right kidney showed old infarcts—the left kidney was markedly enlarged and showed multiple metastatic abscesses. The bladder showed congestion and ecchymosis at the bladder neck and there was inflammation throughout the prostatic urethra. The prostate was of normal size, but showed multiple abscesses with numerous biscuit shaped diplococci on microscopic section. The epididymis showed diffuse inflammation. The seminal vesicles showed swelling and edema, but no abscesses. The left testicle showed purulent fluid in the tunica vaginalis which showed gram negative organisms on smear, not definitely diplococci.

Postmortem Diagnosis. Acute aortic endocarditis, gonococcal; rheumatic myocarditis; bronchopneumonia; empyema, bilateral; acute and chronic epididymitis; acute urethritis; acute pyelonephritis; multiple abscesses of left kidney; infarction of right kidney; acute splenitis; chronic cystitis; acute and chronic prostatitis and vesiculitis; hydrocele, left, infected; basophilic infiltration of posterior lobe of pituitary.

Case 2. A white, married female, aged 28, was admitted August 9, 1922, complaining of chills and fever of three and one half months' duration. She had had a thick yellow vaginal discharge for 18 months following a questionable spontaneous abortion. From the family physician it was learned that there was a definite history of gonorrheal infection preceding the present illness. Her husband had been treated for gonorrheal urethritis at the Boston Dispensary on several occasions. In April 1922 she had an upper respiratory infection and at that time had some dysuria and

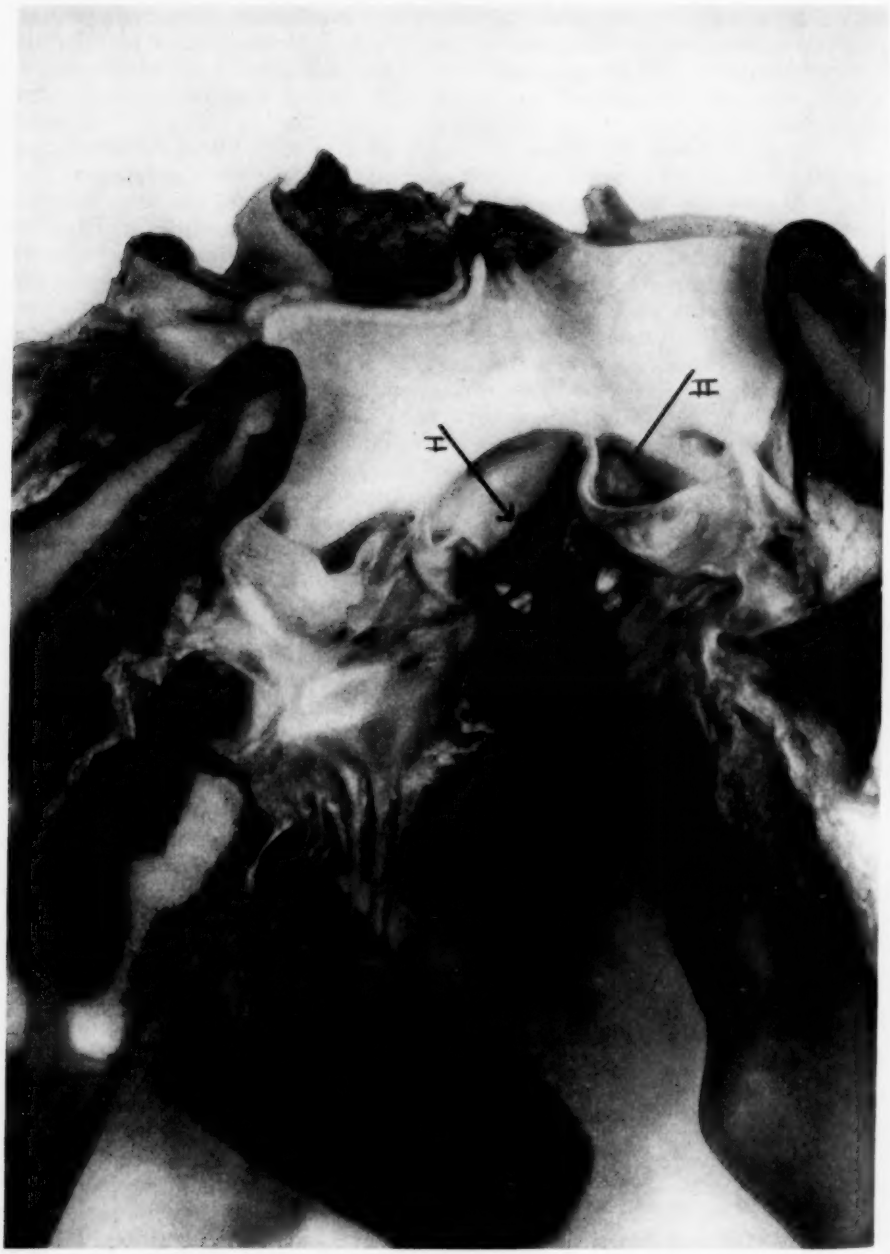

FIG. 1. Arrow I points toward vegetations on ruptured left posterior valve cusp of aortic valve. Arrow II points to vegetation at base of anterior valve cusp.

urgency. Following this there was an increase in the vaginal secretion which persisted until admission. Since April she had noticed an increasing weakness and since May she had had night sweats and severe chills almost nightly. The family history and past history were irrelevant. Inventory by systems revealed no additional data.

Physical examination showed a fairly well developed somewhat wasted woman. The face was pale and thin. On the bottom of the left great toe was a petechial hemorrhage. Examination of the head and neck yielded no relevant findings. The thorax was symmetrical and expanded equally and well. Examination of the heart as reported by Dr. Samuel A. Levine on August 12, 1922 showed a systolic thrill at the apex and a questionable short thrill in diastole. The apex impulse was seen and felt 11.5 cm. from the midline. Left border of cardiac dullness was 12.5 cm. from the mid sternal line; the right border of dullness was not made out. No inincreased submanubrial dullness was made out. The heart sounds were regular and rapid. The first sound at the apex was slightly booming followed by a systolic murmur and an early long diastolic murmur. On approaching the base a different harsher systolic murmur was heard and a typical aortic diastolic murmur along the left sternal border. The radial pulses were equal, regular and synchronous. The blood pressure was 128 mm. Hg systolic and 54 mm. diastolic. The lungs were clear to percussion and auscultation. Palpation of the abdomen revealed that the spleen was easily felt two fingers below the left costal margin. The liver and kidneys were not palpable. There was moderate clubbing of the fingers. A cervical smear showed no gram negative intracellular diplococci. Pelvic examination showed no evidence of pelvic inflammatory disease.

Examination of the blood showed 80 per cent hemoglobin; 3,850,000 erythrocytes; 12,200 leukocytes. A differential leukocyte count gave 83 per cent polymorphonuclears; 12 per cent lymphocytes; and 5 per cent monocytes. Anemia developed rapidly and on October 10 the hemoglobin was 35 per cent and the erythrocytes 1,955,000. Urine examination: Acid reaction, specific gravity average 1.008; albumin varying from slight trace to large trace; sugar negative; the sediment showed many leukocytes and erythrocytes, and many cellular and brown granular casts.

Blood Wassermann negative. Complement fixation for gonorrhea negative. Five blood cultures showed no growth. Electrocardiograms showed left axis deviation.

The temperature curve was of the picket fence type, the fever reaching 105.8° F. and varying between 98° F. and that level. The blood pressure gradually fell and on October 9 was 86 mm. of Hg systolic and 38 mm. diastolic. Transfusion of 300 c.c. of blood from the patient's husband was followed by a severe reaction with temperature rise to 106° F. Sodium cacodylate was given intramuscularly, 0.05 gm., twice daily without altering the course of the disease. The patient died October 18, 1922.

Postmortem examination revealed 1400 c.c. of clear yellowish fluid in the peritoneal cavity with the spleen enlarged and showing two infarcts. The liver extended 4 to 5 cm. below the right costal margin. The pleural cavities contained no free fluid. The lungs showed a definite pneumonia. The kidneys showed cortices thicker than normal and microscopically some of the glomeruli showed adhesions to the capsule and in several thrombi were present. The pericardial cavity contained 210 c.c. of bloody fluid with flecks of fibrin. The parietal pericardium was thickened and covered with a yellowish film of fibrin in places thrown into ridges and folds. Smears from the fibrin showed gram negative diplococci and a few polymorphonuclear cells. Cultures from heart blood yielded a gram negative and gram positive bacillus thought to be terminal invaders as no such organisms were isolated elsewhere.

The heart weight was estimated at 450 grams. The epicardium was covered with yellowish soft exudate thrown up into folds giving a shaggy appearance. The

tricuspid, mitral and pulmonary valves were normal. The aortic valves were somewhat thickened and attached along the margins of the cusps were soft, pinkish vegetations measuring up to 4 to 5 mm. in diameter. Smears from the vegetations revealed a gram negative diplococcus. On blood agar a growth of *Staphylococcus aureus* and diphtheroid bacilli were produced from the vegetations. The entire arch of the aorta seemed dilated. In addition there were several aneurysms with sharply outlined orifices present. There were two aneurysms about 0.5 cm. by 1.0 cm. just above the valve, tending to extend out from the right side of the aortic arch and to bulge into the epicardium. These aneurysms were filled with reddish, granular thrombi. There was a large, sharply delimited aneurysm 2.5 cm. in diameter extending from the bottom of the arch of the aorta. Smears of the friable globular masses of clot in this aneurysm revealed masses of gram negative diplococci, apparently in colony form. A few polymorphonuclear cells were filled with gram negative diplococci. The morphology of these organisms was consistent with that of the gonococcus.

The postmortem diagnosis was acute aortic endocarditis, gonococcal; mycotic aneurysm of arch of aorta (gonococcal); organizing fibrinous pericarditis; hypertrophy and dilatation of the heart; bronchopneumonia; infarct of spleen; ascites and chronic pleuritis.

Case 3. A 24-year-old white male was admitted December 3, 1914 complaining of weakness and fever. Three months before he had had pain, tenderness and limitation of motion in the right shoulder. Two weeks later both knees became painful and stiff. Two months before, he first noticed a daily fever and severe night sweats. There had been a weight loss of 18 pounds. The patient denied gonorrhea or syphilis. The past history revealed pneumonia and pleurisy at 10 years of age.

Physical examination revealed a well nourished white male lying quietly in bed. Examination of the head and neck was negative. The left border of cardiac dullness was 13 cm. from the mid sternal line in the fifth interspace; the right border of cardiac dullness was at the right sternal margin. The heart sounds were regular and rapid. There was a systolic thrill at the apex and a rough blowing systolic murmur was heard at the apex and transmitted to the axilla and to the angle of the left scapula. The mitral second sound was clear. The lungs were clear to percussion and auscultation. The examination of the abdomen showed nothing of note. The liver, kidneys and spleen were not palpable. Blood pressure readings showed 100 mm. Hg systolic and 70 diastolic. The patient was seen by Dr. Henry A. Christian who confirmed the heart findings and made a diagnosis of acute endocarditis. On admission, the hemoglobin was 79 per cent; white blood cells 8,400. Blood Wassermann test positive, two plus. Electrocardiograms were normal on several occasions. Phenolsulphonephthalein test showed 42 per cent excretion of the dye in two hours. On January 4 two petechiae were noted in the right conjunctiva. The patient gradually developed a severe anemia. During the first 11 days the temperature was rarely over 100.4° F., but thereafter it became "picket fence" in type rising as high as 104° F. and being almost continuously above normal. The pulse varied between 90 and 130. On January 19, 1915 a faint diastolic murmur was first heard in the fourth interspace just to the left of the sternum. February 3 a pleural friction rub was heard in the left axilla and back.

He was given antigonococcus vaccine both intravenously and intramuscularly but later developed severe reactions from the vaccine so that it had to be stopped. On February 23 he complained of pain in the left chest and coughed up bright red sputum. He failed rapidly and died in several hours. No postmortem examination was done.

Blood cultures taken on December 4, and December 12, 1914 showed a small short chained coccus growing 3 to 5 cm. below the surface in the dry tube dextrose ascitic agar. No growth was obtained on the plates. Blood culture taken on January 4, 1915 on dextrose ascitic agar plates and tubes showed, after 64 hours in-

cubation, numerous, minute grayish white colonies. Smears showed a small gram negative coccus occurring in pairs and small groups. On subculture growth was obtained on dextrose ascitic agar and in plain ascitic bouillon. On agar slants growth appeared in 48 to 64 hours as fine dew drop colonies. The notation was made "the organism has all the characteristics of gonococcus."

Clinical diagnosis: Acute endocarditis, gonococcal.

Discussion

These cases illustrate the destructive nature of the lesions of gonococcal endocarditis. In the first case one cusp of the aortic valve was practically destroyed. In the second case there were multiple aortic aneurysms in association with an aortic endocarditis with small vegetations.

The difficulty in culturing gonococci from the blood stream is illustrated by the second and third cases. In the second case it was not possible to culture the organism before or after death. The diagnosis in the second case is based on the typical pathology, the appearance and the staining reactions of the organism as seen in the lesions and the history. In the third case there was difficulty in identifying the organism. In the first case cultures were satisfactorily obtained only under partial anaerobiosis.

It is most important to differentiate definitely the organism isolated from the meningococcus because of the difference in therapy and prognosis. Meningococcus endocarditis while rare does occur. Rhoads [19] reported a case of endocarditis due to the meningococcus in 1927 and collected 11 case reports in the literature. In several of these cases no signs of meningitis were observed. One case showed swelling of the joints of the ankles and fingers. Necropsy showed adhesive pericarditis and a cauliflower vegetation on the mitral valve. Several of the cases showed only a vegetative endocarditis but Rhoads' case was marked by its ulcerative character. The vegetative process had ulcerated through the interventricular septum and involved the medial cusp of the tricuspid valve and also the base of the aortic valve. Ross and Greaves [20] report a case of probable meningococcus endocarditis which reacted to specific serum therapy and recovered though with severe cardiac damage.

In our first case the presence of a rheumatic myocarditis was not suspected. There was no past history to suggest such a condition, except for the illness of the previous year when a cholecystitis or coronary occlusion was suspected. Neither of these conditions was diagnosed, as the electrocardiograms and roentgenological studies were normal. There was no gross or microscopic evidence of previous valve damage apparent, which bears out Thayer's conclusion that gonococcal endocarditis is more frequent on undamaged valves.

After studying the various methods in use up to that time (June 1936) in treating gonococcal endocarditis we felt that fever therapy offered a more rational method of treatment than any which had been tried. Careful work had shown that the gonococcus is susceptible to temperatures the human

body can stand. The first patient had a total of seventeen and one-half hours of fever therapy in five sessions, with temperatures of 105.6° to 106.6° F. (rectal) in the first three hour session and 106° to 106.4° (rectal) thereafter. We felt this should have been enough to produce the desired result. However, we did not determine the thermal death time of the particular gonococcus isolated in this case and therefore we cannot state definitely that the amount of fever therapy was sufficient from a theoretical point of view. In future cases this should be done. We do not feel that fever therapy increased the rate of progress of the disease nor did it slow the process.

Summary

1. Three cases of gonorrheal endocarditis are reported. The diagnosis in the first case was made clinically and was proved at autopsy. The organisms were isolated from the blood stream during life and were present in sections from the affected valves at autopsy. The diagnosis in the second case was made clinically. The organism was not isolated from the blood stream during life, but smears from the vegetations at autopsy showed gram negative diplococci and the gross pathology was typical of gonorrheal infection. The diagnosis in the third case was based on the clinical course and history and the isolation of the gonococcus from the blood stream during life.

2. The first case was treated with fever by means of diathermy. A total of seventeen and one-half hours treatment was given at 106° F. (rectal). The second case was treated by general supportive measures. The third case was treated with antigonococcus serum. All three were fatal.

We wish to thank Dr. Israel Kopp for his coöperation in treating this patient with fever therapy at the Boston Psychopathic Hospital.

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BUCKLING OF THE RIGHT COMMON CAROTID ARTERY IN HYPERTENSION *

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In 1925, Brown and Rowntree described a characteristic buckling of the right common carotid artery which is present in some severe cases of hypertension. A review of the literature [1, 2, 5] revealed that such limited recognition has so far been accorded this sign that it seemed opportune to call attention to its frequent occurrence in cases of hypertension and to the mistakes in diagnosis often caused by its non-recognition. We are also reporting two new cases in which buckling of the right common carotid artery occurred. These cases were observed in a study of 48 consecutive hospital cases of white patients who had essential hypertension.

Buckling in such cases consists in a kinking or angulation of the right common carotid artery out under the skin, which buckling is prominent enough to result in a pulsatile mass. This condition must not be confused, however, as has already been done by one writer,[2] with other and far more frequent pulsations in the region of the neck which are seen both in health and disease. What distinguishes buckling from them is the tumor-like deformity which is visible behind the lower third of the sternocleidomastoid muscle. The location of the buckling of the carotid artery as well as its general characteristics often cause it to be confused with carotid and subclavian aneurysm. It should likewise be kept in mind when considering suspected instances of hyperthyroidism.

In all the cases of hypertension with buckling of the carotid artery so far reported the patients have been nonsyphilitic and the buckling has been in the lower anterior part of the neck just above the right sternoclavicular joint. Buckling has never been seen on the left side. Brown and Rowntree's patients were all white women. Beardwood's two patients were negroes, one of them a male. It does not appear, therefore, that the condition is limited to any one race, but we expect that it has a predilection for the female sex. Beardwood's cases are of further interest because, in both of them, the patients were able to state definitely that as far as they knew the pulsating mass was of recent origin.

Brown and Rowntree thought that kinking of the common carotid artery was "the mechanical sequence of the arch elevation, although elongation through increased intra-vascular pressure also contributes to its tortuosity." Figure 1 shows the relative change brought about in this way. It is of interest to note that surgeons operating on tonsils have often reported tortuosity in the internal carotid arteries, and have speculated about the possibility that this tortuosity may represent a reversion to a lower phylogenetic type.

* Submitted for publication December 30, 1937.

These views have been based on the belief that, in seals, the carotid arteries were much longer than the distance they transversed and consequently were not straight. Recently, a very careful study [4] was made of this problem, and it appears that neither in seals nor in any other form of animal life has anybody ever demonstrated a normal tortuosity in either carotid vessel. The theory of reversion to a lower type therefore has no basis. Besides, so far as we know, buckling of the carotid artery has never been reported in patients without hypertension. It would seem, therefore, that the explanation of Brown and Rowntree best elucidates the mechanism of its formation.

In making the diagnosis of buckling one must remember that the condition occurs in cases of hypertension, mostly in women, and apparently only in the right side of the neck. One should attempt to demonstrate elevation

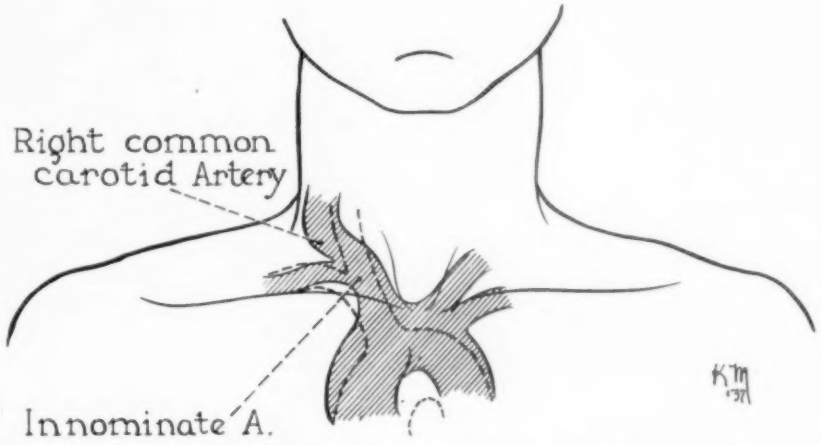

FIG. 1. Buckling of right common carotid artery in hypertension: Increased blood pressure raises the aortic notch, and perhaps elongates the individual arteries. Consequently, the right common carotid artery is pushed outward and upward. The relative position before and after this change is here illustrated. Notice the beginning point of buckling on the heavily shaded carotid artery.

of the aortic arch, either by palpating the episternal notch or by studying a roentgenogram of the thorax. Most important in the diagnosis is actual palpation of the carotid artery itself. In this way one can show the point of angulation, and often establish that the diameter of the vessel has not changed. The pulsation in a buckled artery does not have the expansile quality present in aneurysm. Those who make it a practice [6] routinely to palpate the carotid arteries in cases of suspected cerebral arteriosclerosis have not yet reported the occurrence of buckling in patients with arteriosclerosis but without hypertension. Buckling tends to diminish in prominence when the blood pressure lowers.[1]

CASE REPORTS

Case 1. A Spanish woman, 47 years old, who had had hypertension for the previous four years, registered at the clinic on July 26, 1937. For the previous

nine or ten months she had noticed a pulsating mass in the right lower part of her neck. On admission the blood pressure in millimeters of mercury was found to be 210 systolic and 146 diastolic. When taken at hourly intervals over a period of 24 hours there was a systolic range of blood pressure from 140 to 210 mm., and a diastolic range of 90 to 140 mm.; the mean systolic pressure was 190 and the mean diastolic pressure 115. Examination of the ocular fundi revealed moderate sclerosis and narrowing of the retinal arteries, slight retinitis, but no edema of the optic disks. General physical examination, except for the buckling of the right common carotid artery (figure 2), gave essentially negative results. Urinalysis showed albumin, grade 1, but no erythrocytes, pus or casts. The blood count was normal. Flocculation tests for syphilis by the Kline, Hinton and Kahn technics were negative. A roentgenogram of the thorax and the electrocardiogram gave no additional information. The value for blood urea was 20 mg. per 100 c.c.

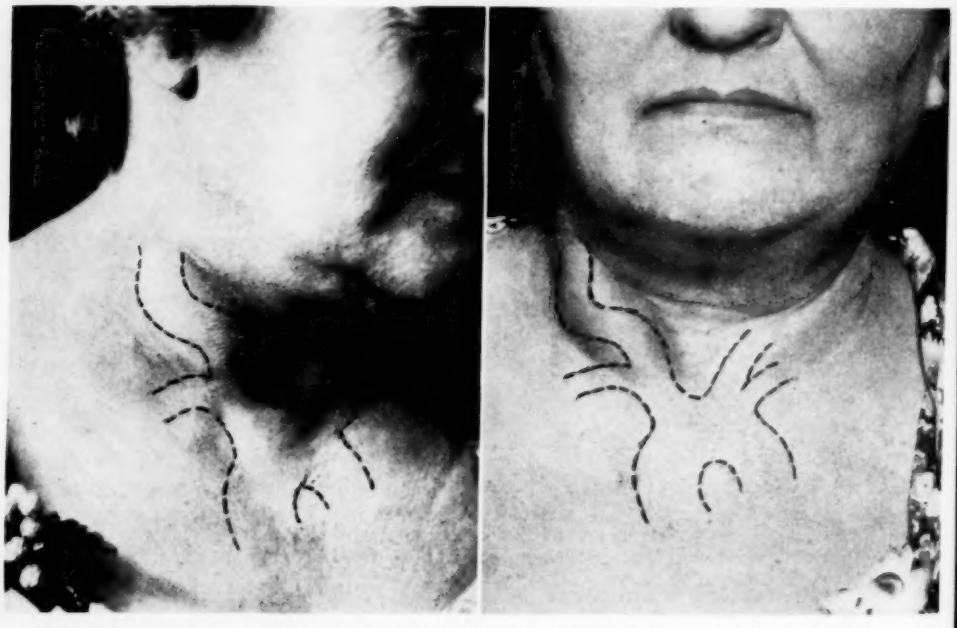

FIG. 2. Buckling of right common carotid artery in hypertension: Showing the relation of the visible bulging to the tortuosity palpated in the underlying vessel.

Surgical treatment was undertaken for the relief of the hypertension. In two stages, on August 10 and September 1, Dr. Adson performed extensive right and left splanchnic nerve resection. He also removed the first and second lumbar sympathetic ganglions and the celiac ganglion on each side. The postoperative course was uneventful. When the patient left the hospital it was noticed that, with the decrease in blood pressure, buckling had become less prominent. At the time of dismissal her blood pressure ranged between a maximum of 145 systolic and 90 diastolic and a minimum of 130 systolic and 80 diastolic.

Case 2. An Irish woman, 44 years old, a year previous to admission had a systolic blood pressure of 250 mm. of mercury, at which time she regarded herself in good health. In the ten months preceding her admission, however, her general health had failed and she gradually complained of increasing weakness and in the last six months had lost 54 pounds (24.5 kg.). When admitted to the hospital on August 2,

1937, she complained of marked dyspnea at rest, moderate orthopnea, frequent palpitations, and constant headache and throbbing at the temples. For the previous two years she had noticed a pulsating mass in the right lower portion of her neck; this mass had not changed in size, however, or given her any discomfort. On general physical examination the patient appeared to be exhausted; she was emaciated and there was cardiac enlargement, pitting edema of grade 2 of the lower extremities, the liver was palpable and buckling of the right common carotid artery was present. The artery could be palpated in remarkable detail. The blood pressure taken at hourly intervals over a period of 24 hours showed a systolic range of 220 to 250 mm. and a diastolic range of 140 to 170 mm.; the mean systolic reading was 230, the mean diastolic 150. Examination of the ocular fundi revealed advanced sclerosis and narrowing of the retinal arteries, marked retinitis, and some edema of the disks. A diagnosis of malignant hypertension was made. Urinalysis revealed albumin, grade 1, but no erythrocytes, pus, or casts. Hemoglobin equaled 80 per cent of normal; erythrocytes numbered 3,780,000 and leukocytes 7,100 per cu. mm. of blood and the differential count was normal. The Kline, Hinton, Kahn and Kolmer tests were negative. The value for blood urea was 18 mg., and for serum proteins 6.1 gm. per 100 c.c. An electrocardiogram showed left ventricular preponderance, normal rhythm, and some myocardial damage. The patient was dismissed from the hospital on August 5, and died at home six days later. Necropsy performed by her local physician is reported to have confirmed the diagnosis made at the clinic.

Comment

In case 1, the pulsating mass in the right side of the neck had been thought to be an aneurysm of the right common carotid artery. More than one physician had seen the patient and this diagnosis had been seriously considered. Careful examination, however, revealed marked buckling of the artery (figure 2). The same comment also applies to case 2. If one has in mind the possibility of buckling of the right common carotid artery, such as frequently occurs in severe cases of essential hypertension, he should have no difficulty distinguishing it from aneurysm. The differentiation of these two conditions, needless to say, is most desirable in view of the very different prognosis in each case. Aneurysm is always, by itself alone, a definite potential liability. Buckling, on the other hand, calls for no special measures; it never enters into the prognosis of the case, the prognosis in such cases depending entirely on the severity and nature of the hypertension.

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SOME DESIRABLE SUPPLEMENTS TO THE PRESENT TRENDS IN MEDICAL INVESTIGATION *

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TRULY the advances in Medicine have been prodigious in the last few generations. These advances have taken place on a broad front and continually make possible the utilization not only of the so-called basic Medical Sciences but also of all branches of sciences for the understanding of disease and, indeed, often for application at the bedside.

The changing situation has developed in internal medicine new attitudes and new standards. It is not too much to say that a new specialty has appeared, that of the medical investigator. Within 50 years, to meet the needs of these medical investigators, Medical Schools and Hospitals have increased manifold and the printed product of this activity has increased many times more.

In these perhaps bewildering changes there seems at times to be a restless activity of feverish intensity. In the training and development of the internist perplexing questions arise. Granted that the internist worthy of the name should participate in medical advances and should, irrespective of age, be a medical investigator, should his work be evaluated on actual publications, on quantity of publications, and what are some of the necessary criteria for the scrutiny of the quality? Or, again, is not " furor scribendi " actually at a premium in the market of medical investigation? Or has there not developed a technic in medical investigation that is stereotype, narrow, and inadequate?

Indeed it would be surprising if, in the midst of rapid and bewildering changes, dealing with possible near or remote application of newly acquired data to that complicated mechanism called man or animal, if you will, errors and faults did not accompany the difficulties. Though the pace is fast, it should be possible to pause in order to strengthen some of the points of weakness of the present system. Obviously, careful objective observation must be the foundation of any investigation whether in Medical Science or in any other branch of science. But unless the scope of these observations is carefully planned and unless the experiments are carefully designed, the labor may be wasted. Indeed the critical observation or experiment is relatively rare. And while we may grant that trial runs are useful in familiarizing the observer with the technic and the field, we have to admit that in the large majority of instances, perhaps approximately 90 per cent, the design or plan or observation or experiment is so bad or inadequate that the entire procedure is really valueless.

If we add to this, those instances in which the statistical requirements are not met, a further wastage is apparent.

* Read before the American College of Physicians, New York City, April 4, 1938.

And finally often hard reasoning is necessary to determine the conclusions to be drawn. This reasoning must satisfy the requirements of logic and must not be colored by wishful or illogical thinking.

The myth of the athletic heart is an excellent example of a product of faulty observation, of the failure to understand and use ordinary statistical principles, and of faulty reasoning throughout, especially in the conclusions based on the physiologic principle that muscular exercise increases the size of the heart, somehow erroneous observations appeared in print aiming to show the increase of the heart under athletic training, especially in colleges. A few cases of cardiac disease or death were cited to furnish the statistical evidence. Then extraordinary conclusions of all sorts were made. However, instruments of precision showed the original observations to be erroneous. But the myth was kept alive by a credence in the statistical evidence although this evidence satisfied no statistical requirement. Indeed, it is difficult to secure adequate data to meet any reasonable statistical requirements for the proof that athletic training in youth predisposes to cardiac death 20 to 40 years later. Certainly a little thought indicates many other factors that might affect the heart in addition to college athletics. Of course, any conclusions based upon such faulty observations and statistics are worthless. But highly colored conclusions were drawn. Unfortunately the myth still lives although in a feeble state.

Medical science is a young and new science. It aspires to a place alongside of the physical and natural sciences. And there are careful workers in the laboratory and in the clinic whose technic places them on a par with the scientists in other fields. In clinical medicine, Hippocrates, Jenner, Oliver Wendell Holmes, Reginald Heber Fitz, and one of the Fellows of the American College of Physicians who is on this program, James B. Herrick, are but examples of a considerable group. Relatively speaking this group is small and there is real danger that there may be a separation between this group and the other medical investigators. There ought not to be a dual standard, one good and the other debased, with the probable result that medical science will settle into the soft mud of careless methodology.

Much has always been made of the importance in medicine of observation. Every medical student is impressed by the paramount necessity of the trained use of touch, sight, hearing, smell and occasionally of taste. There are many mechanical devices to assist those senses. The use of the stethoscope is a classic example. The visual aids, which include the microscope, ophthalmoscope, cystoscope and the like, have been a large factor in modern medicine. It is indeed hard to conceive of medical science without the microscope.

But in the present onward rush of medical progress, other faculties are needed to supplement these observational senses. Hippocrates and his group were masters in the art and science of observation. We have coming down

to us, after two thousand years, many clearly defined clinical pictures as true today as then. But the conclusions of Hippocrates, while based upon accurate and repeated observations, were arrived at by careful deductions. These deductions were as carefully controlled as the observations themselves. Likewise, Jenner observed cow pox in milk maids. By the simple statistical collection (no doubt unconscious on his part) of these data, Jenner noted in a sort of statistical fashion that most milk maids contracted cow pox. His (still probably unconscious) statistical data showed that human or small pox was rare among milk maids; or, in other words, there was a high correlation between the incidence of cow pox and the absence of small pox. Jenner next (unconsciously doubtless once more) called upon another faculty or trait or whatever you care to call it of his mind, and inferred or deduced that the cow pox protected against small pox. If his observations were correct and if there were no unknown disturbing factors, this deduction was logical and it was so subsequently proved by the accumulation of abundant statistical data and the establishment of a high correlation of absence of small pox and the presence of cow pox.

In some ways, medicine has not changed in the development of the use of statistics or the use of deduction since the days of Hippocrates or of Jenner.

We have done decidedly better in regard to statistics than in regard to deductive reasoning. The simple statistics of Hippocrates and Jenner have served their purpose. The same is true of the simple correlations of Osler and Cabot. Most of us are now familiar with the punched cards of statistical technic. It took us a long time to realize that mortality figures in pneumonia had to be broken up into age groups and also into types of the infecting pneumococcus. Then, too, there may be a yearly or seasonal variation. Nevertheless, many men assert that, irrespective of statistics, certain procedures in pneumonia do good and are accompanied by a lessened mortality.

At one time, based upon electrocardiographic evidence, it was urgently advocated that digitalis be used in every case of pneumonia. Without statistical proof and without sound reasoning, the use of digitalis became, almost overnight, practically a routine procedure in the treatment of pneumonia. Subsequently, however, careful clinical studies under adequate statistical control indicated that the routine of employment of digitalis was actually detrimental to the average case. From time to time, it is the fashion to deride statistics, but the observational data which go into the statistical treatment (like the beef that goes into the can) are not changed by the process. The method is less faulty than the data. It is a long road to prove statistically the benefit of a therapeutic procedure in pneumonia. Very likely, there are still other unrecognized variables besides age groups and types of pneumonococci. Animal experiments and test tube researches are illuminating but the final answer to the query of the beneficial effect of a procedure in pneumonia in humans must be statistical.

It is certain that if data do not meet simple statistical requirements, it is quite futile to try to draw conclusions from them. In the laboratory and at the bedside, we may usually safely assume that the actual observations are accurate. It is necessary as the next step that these observations meet certain statistical requirements. Then, as a final step, deductions are made from these data.

It must be remembered that a diagnosis is rarely an observation. Pneumonia as a diagnosis is not an observation. It is a deduction.

While it is true that many of our medical errors are derived from failure to use statistics correctly, and that often means an inadequate amount of data, nevertheless, the greater bulk of our medical errors and medical difficulties are derived from faulty reasoning processes. We make many unjustifiable assumptions. We assume that we know certain facts which we actually do not know. Improper conclusions or deductions may be readily made from data which are accurate enough. For example, for many years it was argued that since malaria existed in little swamps and marshy places, therefore it was the dampness which caused the malaria.

There is one form of faulty reasoning or faulty logic which is unfortunately common in medical literature. For example, it is known that all cases of pernicious anemia have an absence of free hydrochloric acid in a gastric analysis. It does not follow, however, that all cases of absence of hydrochloric acid have pernicious anemia. Again, in pernicious anemia, most of the cases respond to liver therapy. It may be argued that liver therapy is a therapeutic test for pernicious anemia, but one must not argue that no cases are to be diagnosticated as pernicious anemia if they do not respond to liver therapy and that therefore liver therapy is always successful in pernicious anemia.

Sometimes, our so-called "medical science" leads us astray as it did temporarily in the use of codliver oil in rickets. The clinical data were entirely correct as to the value of codliver oil in rickets. However, until we really understood about vitamins, it was the habit of some men to deride those excellent clinical conclusions. It is chastening, as well as valuable, to recall the derisions with which the profession generally greeted the observations of Oliver Wendell Holmes on the transmission of childbed fever, a brilliant bit of correct observation with statistical treatment of those observations and with the resulting correct deduction.

From the very nature of things, clinical observations are complicated. Man is ever variable. Controls may be difficult. There are always unknown variables. Nevertheless, clinical material has always furnished excellent illustrations of the best and most scientific types of medical investigation. Likewise, as investigation in pure science becomes more complicated, it seems to partake of some of the difficulties herein discussed. I venture this somewhat timidly and indeed humbly. I let others discuss the difference of opinion concerning the cosmic ray, concerning atomic explo-

sions, or concerning those chemical formulae that fill a blackboard only to disintegrate and reform at the waving of a chemical wand. Or do they?

A great many medical beliefs, medical procedures, medical routines, and the like are based upon what we like to call the results of our logical reasoning. For example, should one use ice baths to reduce fever? Obviously there are many considerations and we finally gave up ice baths as an inevitable logical procedure in fever. Again, if a person is infected with a few microörganisms, is it logical to assume that he will be less sick than a person who is infected with many microörganisms? As an example, is it logical to assume that a person infected by typhoid bacilli in the water will be less sick than a person infected with typhoid bacilli in milk? Presumably the milk will carry more bacilli than the water. Let us grant that the virulence of the microörganisms is the same and let us grant that the series of cases is large enough to iron out the variability of possible special groups of immunes or partial immunes. The answer must be "No" of course. Again, is it logical to assume that bacterial vaccines are useless in existing infection? Of course, the argument is that the living bacteria would produce immunity if it is to be produced and therefore that bacterial vaccines are useless. But this illustration, like the others, concerns not the process of logic itself but the assumption of the argument. It is not known whether changed bacteria, as they are in vaccines—dead, devitalized, attenuated or what not—have necessarily the identical effect in immunity production possessed by the living bacteria and indeed this may vary with different forms of bacteria and indeed in different individuals either under the same or different circumstances.

Perhaps the commonest illustration concerns the prevention of the common cold by vaccine. We do not know the causative agent of the common cold and therefore the bacterial vaccine used to prevent colds does not contain it and is it therefore necessarily illogical to give these bacterial vaccines as a preventive of colds? Of course, the answer must be that it is not necessarily illogical although there is no evidence that it is logical, because immunity to the cold may be produced by non-specific therapy.

Some years ago, the effect of liver and other substances in the diet on the anemia in dogs secondary to bleeding was studied. Of course, it had been urged that it was illogical to give meat in pernicious anemia because of the absence of hydrochloric acid. Because anemia secondary to hemorrhage in dogs and pernicious anemia were quite separate entities, it seemed unlikely that liver therapy would be of benefit in pernicious anemia. Of course, that happened to be exactly wrong. In this case, the feeding of liver and other substances in anemic dogs was one thing and liver and allied therapy in pernicious anemia was quite another thing. Or, at least, it so seems now.

Everyone knows that among all individuals wishful thinking, or the rationalization of what we desire, is very common. We know what we want and therefore build up arguments in its favor.

One could give many illustrations of simple errors in reasoning mostly based upon the fact that in the reasoning only one instead of several possibilities are considered. The type of thing to which I refer is the reasoning that in pneumonia there is usually a high fever, therefore any high fever may mean pneumonia. Of course, such an illustration seems absurd on the face of it. On the other hand, physicians do not hesitate to argue that because appendicitis is often accompanied by a leukocytosis, therefore if there is any leukocytosis the diagnosis is appendicitis.

One hears and reads the statement that infections cause leukocytosis but with two exceptions—one, the infection may be so overwhelming that there is no leukocytosis; two, the patient may be so debilitated as not to be able to produce the usual leukocytosis. In reality, it is true different types of infections tend to produce, from the circulating toxins, etc., different effects upon the hemopoietic system and therefore different blood pictures. Some infecting microörganisms have little or no effect upon the leukocytic count; other microörganisms affect the lymphocytic system rather than the polynuclear system. Indeed, one can get results from other circulating poisons which are quite similar to the circulating toxins of microörganisms. The point is obvious, of course, that the blood picture is not in itself diagnostic of any precise disease, but indicates the effect of certain reactions on the blood-forming organs.

Again, many tests have been devised, and much time has been wasted, merely because the advocates of these tests, finding that the tests were positive in some particular disease and negative in normal people, at once concluded that the test was diagnostic of this disease. In many instances, the test is merely positive for some general type abnormality as fever. A vast amount of literature has been accumulated in regard to the so-called "blood sedimentation rate." Following the loose form of reasoning just described, the blood sedimentation rate was supposed to be diagnostic of a wide variety of conditions—pregnancy, cancer, rheumatism, etc. It was pointed out, when the sedimentation rate was being discussed in the early stages, that in normal people there was a normal sedimentation rate. In many, but not in all diseases, there seemed to be an alteration in the sedimentation rate. It was merely one of the many things that happen; the human organism is not normal. Changes in a sedimentation rate, in the same individual, may be of some value in determining the course of the disease and indeed the prognosis. After a good many years, that is the conclusion which has emerged out of a huge mass of contradictory and conflicting conclusions and summaries. Even now, undue dependence is placed upon this test; in the first place because there is no specificity about this test and, in the second place, there may be some other condition which is altering the rate besides the condition which is being studied.

In every field of medicine, one could multiply the argument for the necessity of careful and thorough deductive reasoning. As I have pointed out elsewhere, the examination of the urine is not a perfect test for nephritis

or diabetes. Indeed, the examination of both the blood and the urine, while giving us a great deal of information, may be neither dependable nor precise. The reason for this is that the morbid processes are within the cells and the blood itself is only one step nearer the cells than is the urine. There is a good deal of evidence that the blood is used for a sewerage system and does not always reflect exactly the condition of the cell. Furthermore there may be other factors which may affect the blood and urine figures. For example, a Marathon runner will present a urine of acute nephritis. A starving patient will show a blood non-protein nitrogen which is that of uremic coma. Furthermore, if he is starving, and has enough acidosis to produce a high non-protein-nitrogen, he may also present a urinary picture of nephritis. It would be very easy to multiply these casual observations, selected at random, in the field of medical investigation but, suffice it to say, every procedure is subject to each of the factors which we have considered.

Even if we are careful of our observations, of our statistics and our logic, we must admit that many of the processes which we are studying are very little understood. From time to time that will result in seeming refutation of the value of logic. I have in mind the so-called "Wassermann" test, which is an adaptation of the complement fixation test. It was originally considered to be a specific test because, presumably, a specific antigen was used. We now know that the antigen is not specific, yet the test runs as closely to being perfectly accurate as one may expect on the law of chances. Of course, somewhere there is a reason for it. While we accept with gratitude the extraordinary accident that has given us such an extraordinarily useful test as the Wassermann test, we can use this experience as a chastening example of our fundamental ignorance and it points to the necessity of avoiding at all times a completely dogmatic viewpoint.

Hard, sound reasoning and logical deduction can be developed as a part of the necessary equipment of the medical investigator. They are as vital as accurate observation or adequate statistical data. Wishful thinking and rationalization belong to the same category of scientific sins as erroneous observations and misleading statistics. It should be and, indeed, must be the only satisfactory destiny of Medicine, to be the Science of Medicine. As such, the Science of Medicine will, we trust, be grouped with the Physical Sciences and the Natural Sciences. We like to think that we are close kin to these somewhat rigid sciences wherein data are factual and statistically adequate, and reasoning is as sound and relentless as the limitations of the present knowledge permit.

CASE REPORTS

A CASE OF ATELECTASIS OF THE RIGHT LOWER AND MIDDLE LOBES WITH BRONCHOSCOPY DEMONSTRATING SPINDLE CELL SARCOMA OF THE RIGHT MAIN BRONCHUS *

By Otto S. Baum, M.D., John H. Richards, M.D., and Maxwell D. Ryan, M.D., *New York, N. Y.*

Case Report

The patient, R. Z., is a 29 year old American housewife, admitted to the Second (Cornell) Medical Division of Bellevue Hospital on March 16, 1938, complaining of right-sided chest pain, cough, and 15 pounds loss of weight during the preceding six weeks.

History: She had always been well, recalling only measles and chickenpox. Her mother had died of diabetes; the family history otherwise was negative. She is married, has two children living and well, having had one miscarriage. Review of her history by systems shows no relevant factors.

Six weeks before entry she developed an upper respiratory infection, diagnosed pneumonia and pleurisy by her family physician. She recovered from the acute episode, but had a persistent cough since, productive of whitish sputum in small amounts, never blood tinged. She lost about 15 pounds in weight during this time. There have been no night sweats, but afternoon fever up to 102° F. was noted. She complained frequently of sharp pains in her right chest, located more often posteriorly, and worse with respiration though steady once they arose. At times she felt as though her heart were beating in her right chest, but the exact date of onset of this sensation is uncertain. She has not been dyspneic, orthopneic or cyanotic.

On the morning of admission she complained once more of severe right-sided chest pain, associated with nausea and vomiting of previously ingested food. Her physician at first thought she had a minor gastrointestinal disturbance, but after persistence of the chest pain, sent her to the hospital for observation and treatment.

Physical examination: On admission this thin white female appeared to be chronically ill. There was moderate pallor of the skin, conjunctivae and mucous membranes. She was not dyspneic or orthopneic, or cyanotic, but complained of severe pain and a sense of tightness in her right lower chest posteriorly. The temperature was 99.4°, the pulse rate 88, the respiration rate 24, and the blood pressure 114 mm. of Hg systolic and 76 mm. diastolic.

Important abnormalities noted were as follows: The trachea was deviated markedly to the right. There was limitation of expansion of the right chest. The heart was shifted toward the right, the point of maximal impulse being poorly felt 4 (?) cm. to the left of the midsternal line. Heart sounds were heard much better to the right of the sternum, especially those at the base of the heart; they were of good quality, with A_2 greater than P_2.

Examination of the lungs showed dullness over the upper third of the right lung field anteriorly and posteriorly, flatness over the lower third of the right chest

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anteriorly, extending higher in the axilla and posteriorly. Breath sounds over the upper third on the right were loud, bronchovesicular, with marked increase in tactile fremitus, voice sounds, and with whispered pectoriloquy over this area. Rare post-tussic fine râles were heard anteriorly over this area. Over the area of flatness the breath and voice sounds were absent but tactile fremitus was present though markedly diminished. The left chest was normal and the remainder of the examination entirely negative.

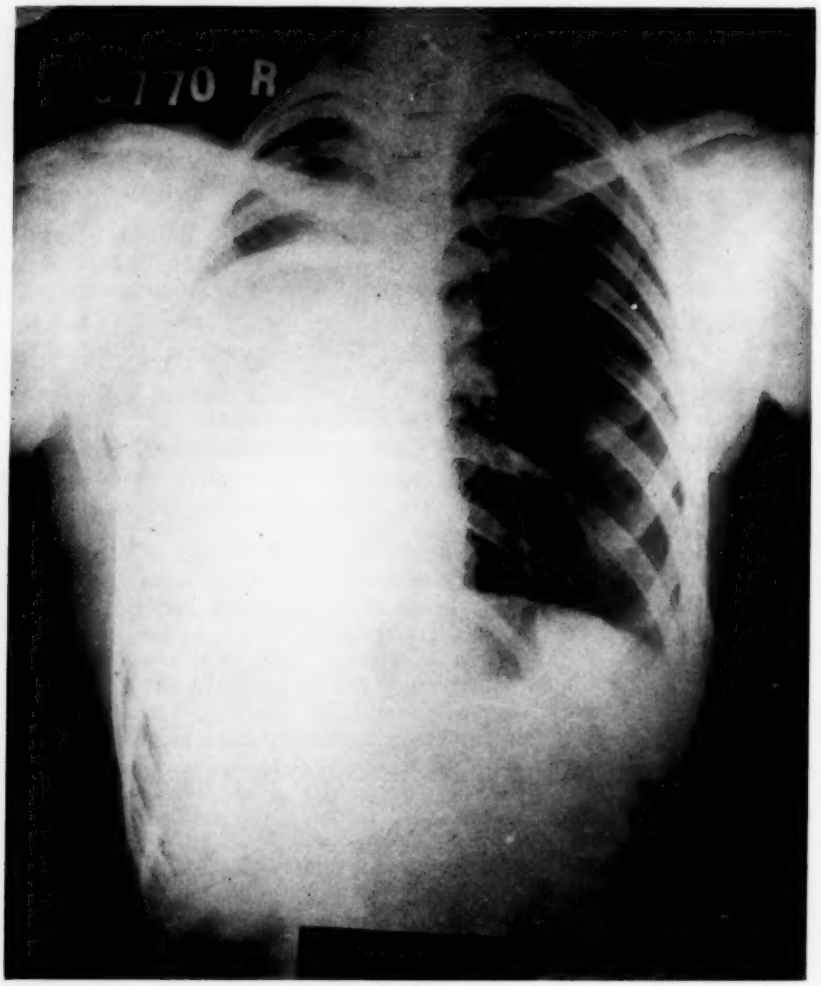

FIG. 1. Roentgen-ray, March 16, showing lower two-thirds of the right lung obscured by dense shadow and heart and mediastinum drawn to the right.

Laboratory findings were as follows: Urine entirely normal. White blood count 8500; a differential count showed 63 mature and 16 immature polymorphonuclear neutrophiles, 21 lymphocytes and 1 monocyte. The red cell count was 4.6 millions, the hemoglobin 85 per cent (Sahli). The sputum showed no acid fast organisms. The blood Wassermann test was negative. Blood non-protein nitrogen was 31 mg. per cent.

Fluoroscopy on the morning following admission showed the heart to be displaced toward the right, its left border about 1 cm. beyond the left sternal margin. The trachea was deviated toward the right. The right lower lung field was completely obscured by a density having the appearance of an elevated diaphragm plus collapsed lower and middle lobes. The apex was clear. (Figure 1.)

It was thought that the patient had a plug of tenacious mucus or of granulation tissue in the bronchus to the right lower and middle lobes and immediate bronchoscopy

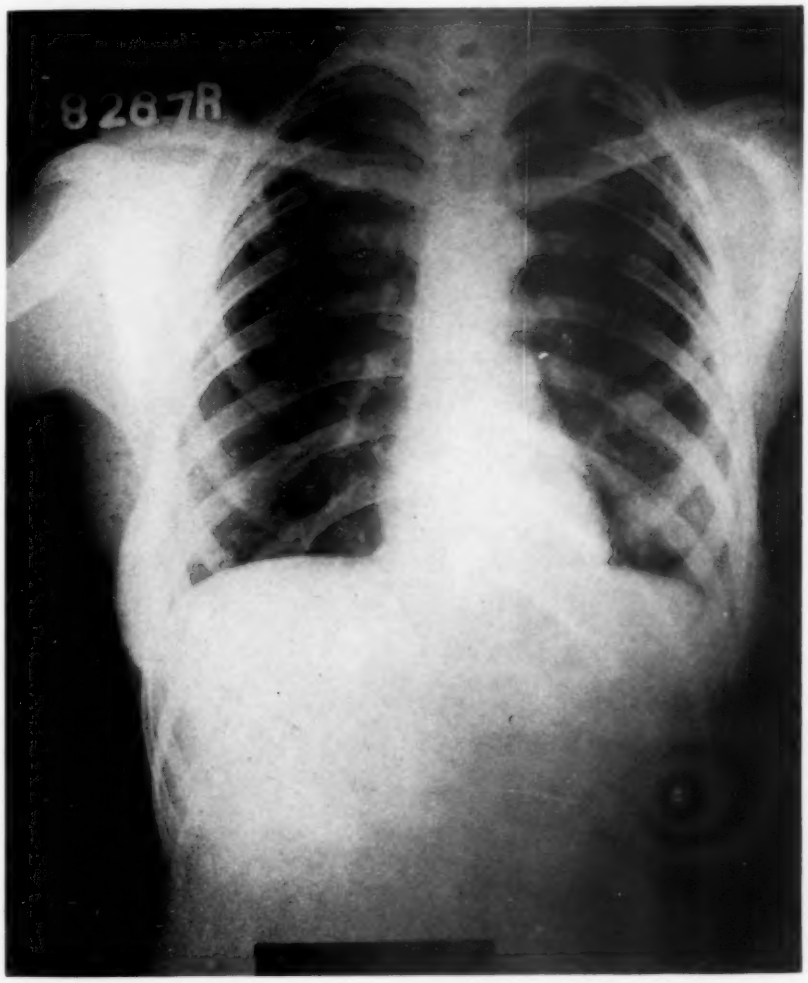

FIG. 2. Roentgen-ray, March 22, showing rapid return to normal of the right chest after bronchoscopy had cleared the bronchial lumen.

was deemed advisable and was performed by the Bronchoscopic Service. "The bronchoscope was passed. Just below the carina of the right main bronchus a mass of polypoid tissue, soft and friable, was seen occluding the right main bronchus. A piece was removed by forceps, the remainder being suctioned out. Air was noticed coming from the main bronchus at the conclusion of the procedure."

The patient immediately felt relieved, with complete disappearance of the chest pain, a sensation of "lightness" in the chest, and easier respirations. Three hours

FIG. 3. Magnification 110. Low power microscopic view of tumor tissue.

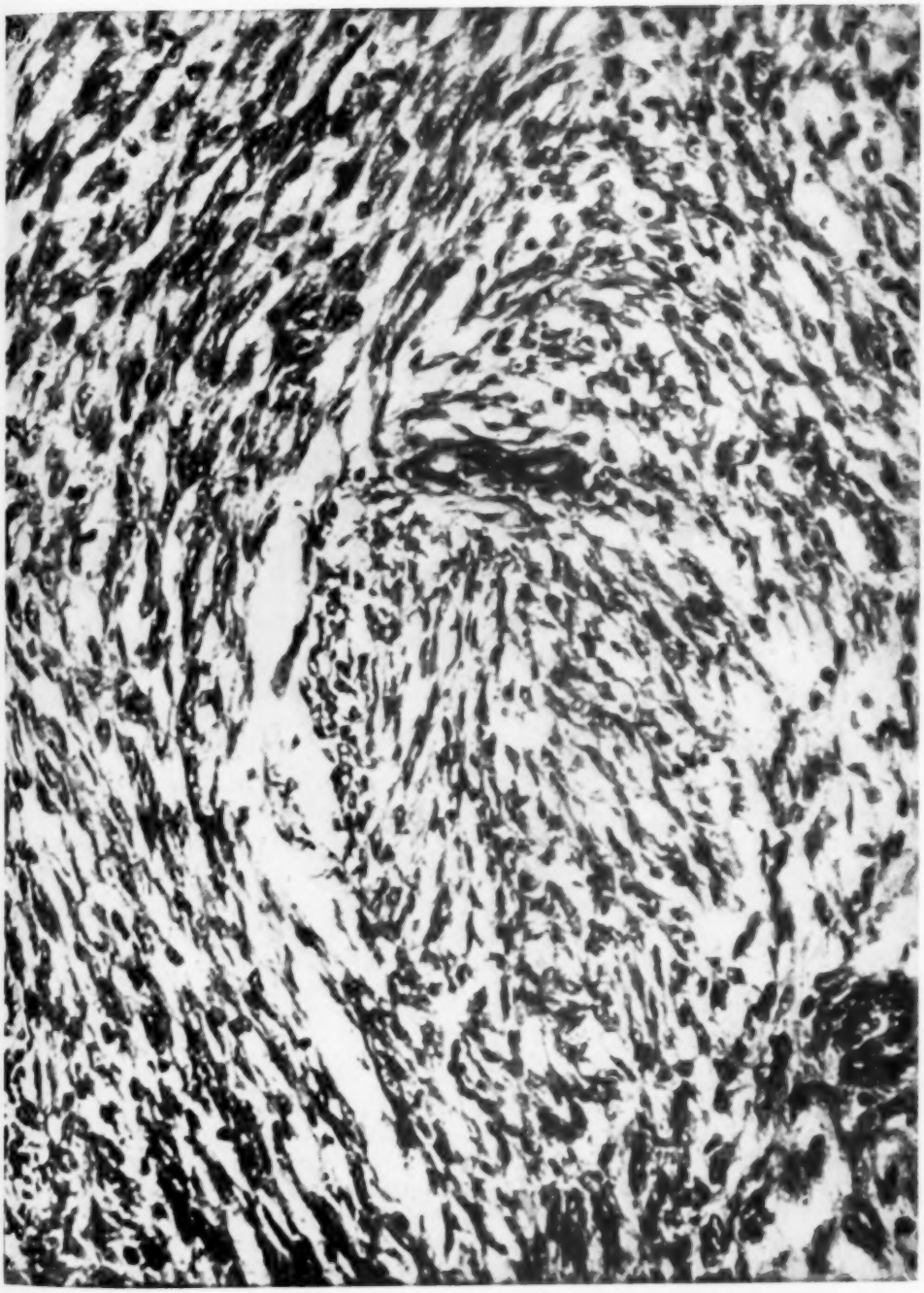

FIG. 4. Magnification 390. High power microscopic view of tumor tissue.

after bronchoscopy she coughed up a large mass of tissue, grayish, smooth, resembling that seen at bronchoscopy, surrounded by blood clot, in the form of a bronchial cast. Examination of the chest at this time showed a definite shift back to normal of the mediastinum, and this progressed rapidly so that seven hours after bronchoscopy the chest signs were practically absent, and 24 hours after bronchoscopy the mediastinum by fluoroscopy was seen to be in the normal position and the lungs were clear. These findings were confirmed by a roentgen film taken on the fifth day following bronchoscopy (figure 2). This state persisted throughout the remainder of the patient's hospital stay, with normal physical findings over the entire chest from 24 hours after bronchoscopy to the day of discharge.

Roentgen-ray reports: March 16, 1938. "Complete obscuration of the pulmonary markings of the lower two-thirds of the right lung field. There is retraction of the

FIG. 5. Bronchoscopic view, March 30, of neoplasm encroaching on the lumen of the right main bronchus. (Drawing by Dr. C. Tannhauser.)

mediastinal contents to the right. This is mainly due to atelectasis. Underlying lung pathology cannot be commented upon."

March 22, 1938. "No infiltration or consolidation of either lung. There is no evidence of neoplasm."

Pathological report: The bronchoscopic biopsy, as well as section of the piece of tissue coughed up by the patient both were reported as spindle cell sarcoma. (Drs. Gustafson and Symmers.)

"Microscopic section shows ciliated columnar epithelium, with immediately subjacent tissue consisting of dense, highly cellular fibroblastic tissue. Cell type is mainly spindle, arranged in no definite pattern." (Figures 3 and 4.)

On March 30, 1938, 13 days after the first bronchoscopy, a second bronchoscopy was performed by the Bronchoscopic Service, "The bronchoscope was passed. There was a mass of tissue filling about one-third the lumen of the right main bronchus, just about 1 cm. below the carina, and ½ cm. below the right upper lobe bronchus. The orifice of the right upper lobe bronchus was swollen and edematous. The mass

described was nearly all aspirated with suction. Straining of the fluid revealed a soft myxomatous mass of tissue." (Figure 5.)

After consultation with the Radiation Therapy Division, deep roentgen-ray therapy to the right chest was started, and is being continued.

The patient was discharged from the hospital on April 7, 1938, to return for deep roentgen-ray therapy and follow up, as well as future bronchoscopy.*

Comment

This case is presented primarily to demonstrate the necessity for early bronchoscopic examination in bronchial lesions interfering with normal respiratory mechanics. It will be noted that the patient was bronchoscoped immediately after the diagnosis of atelectasis had been made. The dramatic and gratifying result both to the patient and the physician—even in view of the doubtful outcome in this particular case—warrants such examination.

No case report of this kind is complete without the postmortem examination, and the significance of the pathological findings is lessened by the absence thereof. However, in this case the corroboration of findings on repeated biopsies of the tumor, as well as the absence of clinical findings of a primary tumor elsewhere, seem to us to warrant its description as an intrinsic primary bronchial neoplasm.

Sarcoma of the lung is an exceedingly rare tumor. Lenk [22] estimates that 0.009 per cent to, at the most, 0.02 per cent of all autopsies show this lesion. Boschowsky (quoted by Lenk [22]) in 1912 in summarizing the literature up to that time found only 63 cases in the preceding 55 years. Adler in 1913 (as quoted by Pilot [26]), found 94 cases of sarcoma reported in the literature but maintains that most of these fall into the category of round cell carcinoma. In the more recent literature, rare individual case reports are noted. Lenk, in a series of 5600 autopsies, between 1922 and 1927, found only one case. At the Massachusetts General Hospital, Mallory [3, 4, 5, 6] reports one case in 800 autopsies, and maintains that primary fibrosarcoma of the lung is among the rarest of tumors, though pleural and mediastinal sarcomata are relatively more common, particularly neurofibrosarcomata. Ball [2] in reviewing the literature from 1900 to 1931, finds 13 cases of primary sarcoma of the lung. Other individual case reports are those of Divis,[9] Roberts,[27] Collier,[8] Rosenblum and Gasul,[28] Pilot,[26] Sach,[12] Jessop,[12] Herzmann,[14] Otten,[21] Herrnheiser,[13] et al. Rosenblum and Gasul [28] review the pediatric literature, finding, in addition to their case of a primary sarcoma of the lung in a 29 month old infant, two other cases in infants, and 11 cases in older children. Ewing [11] suggests that the histological appearances which inflammatory lesions, and overgrowths of reparative tissue may assume, often simulate round and spindle cell sarcomata.

Three general types of sarcoma are recognized by Lenk [22]: (*a*) Primary sarcoma nodule—interlobar or peribronchial; (*b*) lobe sarcoma—involving usually the entire lobe of the lung; (*c*) primary sarcoma of lymph nodes.

Of these, the second is considered most frequent by Lilienthal.[23] The source of the sarcoma is usually the peribronchial or interalveolar connective

* Since the time of writing this report the patient has received a course of deep roentgen-ray therapy. Subsequent bronchoscopies have revealed shrinking of the endobronchial portion of the tumor, so that the last bronchoscopy on August 17, 1938, showed merely slight elevation and reddening at the tumor site. Clinically the patient is well, and frequent fluoroscopies have shown no pulmonary or peribronchial lesions.

tissue, as well as the interstitial connective tissue of the lymph node. (For purposes of clarity lymphosarcoma is not discussed.) Tuffier is quoted by Lilienthal [23] as claiming that sarcomata originate usually in a bronchus, but this is disclaimed by Lenk.[22] The latter insists that bronchostenosis is a very rare phenomenon; that when it occurs it is due most often to external compression (cases of Frankel and of Assman) and only rarely to penetration into the bronchial lumen (cases of Kohler). For this reason atelectasis is also an uncommon occurrence.

For the same reason a review of the literature revealed only one case—that of Herrnheiser,[13] of sarcoma of the lung diagnosed by bronchoscopy (excluding one case of lymphosarcoma reported by Vinson [30]). This is in marked contrast to the relatively frequent occurrence of benign endobronchial neoplasms of mesenchymal origin. The first benign tumor removed successfully by the bronchoscopic route was an endothelioma, reported in 1917 by Chevalier Jackson.[16] Among other bronchoscopists reporting such neoplasms are Jackson and Jackson,[17, 18] Jackson and Konzelmann,[19, 20] Myerson,[25] Ashbury,[1] Morlock and Pinchin,[24] Welt and Weinstein.[32] In this group disturbances in respiratory mechanics resulting either in emphysema or atelectasis depending on the nature of the bronchial obstruction, are frequent. The most notable in this series is the case of Ashbury [1] with three repeated massive collapses due to a benign neoplasm.

The treatment of pulmonary sarcoma is naturally unsatisfactory, though considered by some to be less so than that of pulmonary carcinoma. Successful lobectomies have been reported by Herzmann [14] and Divis,[9] though in the latter case recurrence was observed after two years. Herrnheiser [13] reports complete cure following deep roentgen-ray therapy of a case of an infiltrating mesenchymal neoplasm, arising probably on the basis of malignant degeneration of a polyp. Implantation of radon seeds in sarcomas extending into the bronchus, as well as electro-coagulation, have been suggested, but it is well to keep in mind the case of endothelioma of Welt and Weinstein,[32] which was treated by radium implantation, and which at necropsy showed a tracheo-esophageal fistula. The fact that most of the cases reported are necropsies indicates the discouraging nature of the therapeutic results.

In our case, deep roentgen-ray therapy was initiated after the startling discovery that in 13 days the tumor had grown sufficiently large to occlude one-third of the diameter of the main bronchus. It is hoped that this method of therapy, in combination with repeated bronchoscopy and possibly electro-coagulation of the base of the tumor, will prove successful in averting the otherwise fatal outcome.

Summary and Conclusions

1. A case of spindle cell sarcoma of the right main bronchus, with bronchoscopic demonstration of atelectasis of the right lower and middle lobes, is reported.

2. A brief summary of the literature on sarcoma of the lung is given.

3. Sarcoma of the lung is found to be a very rare tumor, occurring in only from 0.009 per cent to 0.02 per cent of all autopsies; endobronchial sarcoma with atelectasis is found to be rare even among pulmonary sarcomata.

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AN INTRACRANIAL CAROTID ANEURYSM OF LONG DURATION*

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DURING the past decade, numerous articles dealing with intracranial arterial aneurysms have been published.[1-12] Because, with a rare exception,[13] they have all appeared in special journals it is likely that many physicians are still unfamiliar with this not infrequent condition. In 1102 consecutive necropsies (excluding stillbirths), in which the head was examined, the records of The Jewish Hospital of Brooklyn reveal 9 aneurysms of intracranial arteries. This is an incidence of 0.8 per cent. Other writers give an incidence of 0.5 per cent to 1.5 per cent.[14]

Etiologically, aneurysm of the intracranial arteries may be classified as arteriosclerotic, congenital, mycotic, syphilitic and traumatic. In arteriosclerosis, the uneven fatty and fibrous changes in the vessel wall probably result in weakening, bulging at some point and, consequently, the formation of an aneurysm. Often, this is hastened or aggravated by the associated vascular hypertension. The congenital group comprises those aneurysms which occur in young people and to which no specific cause can be assigned. It is agreed by a number of observers[9, 15, 16, 17] that these aneurysms are based upon a defect in the media of the arteries, frequently at the points of bifurcation. Mycotic aneurysms are caused by inflammation of the vessel wall following the lodgment of an infective embolus from the left side of the heart. Syphilis is regarded by most authors as an insignificant cause of intracranial aneurysm. It cannot attack the smaller intracranial vessels through the vasa vasorum, for these nutrient channels are not present except in arteries the size of the basilar. Should it affect the vasa vasorum of a vessel as large as the basilar, it might weaken the wall of the artery and permit aneurysmal formation.[18] In the smaller vessels the syphilitic lesion, being a productive one, usually causes occlusion rather than aneurysm. In the traumatic group belong those aneurysms which follow fractures at the base of the skull or other mechanical injuries inflicted upon intracranial arteries. Most of these aneurysms, being arteriovenous, are not included in this discussion.[19] A case of pure arterial aneurysm following a head injury in a three year old boy was included in the series of Dial and Maurer.[20]

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The clinical manifestations of intracranial aneurysm are governed by the underlying disease and by the effect upon neighboring structures. The symptoms of the underlying disease cannot, by themselves, establish the diagnosis of intracranial aneurysm. The signs evoked by changes in the neighboring structures fail, likewise, to certify the diagnosis, for most of them may be produced by any expanding lesion within the skull [21, 22] and by certain inflammatory processes. Especially is this true before rupture of the aneurysm has occurred. It is not surprising, therefore, that the diagnosis of intracranial aneurysm was at first made only at postmortem examination, and this despite a number of reports in the early literature, among them one in 1859 by Gull of 62 aneurysms [23] and one in 1890 by Pitt of 19 aneurysms.[24] The monumental study of Beadles [25] covering 555 cases and the work of Fearnsides [26] stimulated a more lively suspicion of the lesion during life. Its diagnosis before death was proved feasible by a number of case reports.[6, 8, 27, 28, 29]

The symptoms produced by a small aneurysm may be negligible until rupture occurs. The disturbances caused by a large, unruptured aneurysm depend upon its relation to cranial nerves or to special sites in the brain and upon whether the aneurysm irritates or destroys the structures upon which it abuts. Here, a knowledge of neuro-anatomy and physiology often serves to localize the lesion. Further and more precise evidence of intracranial aneurysm has recently been sought in roentgenographic studies, simple [30] or combined with endarterial injection of radiopaque substances.[11] To Dyke [30] the following signs confirmed the diagnosis of aneurysm of the carotid artery: a curvilinear shadow above and slightly to one side of the sella turcica, due to calcification within the wall of the aneurysm; unilateral erosion of the sella turcica; enlargement of the sella; unilateral enlargement of the optic foramen and superior orbital fissure; erosion of the margins of the carotid canal; displacement of the pineal gland. In his series of cases no necropsies were reported.

Even when accompanied by distinct localizing signs, the vast majority of intracranial aneurysms are not diagnosed until they have ruptured. Then, the sudden hemorrhage into the subarachnoid space produces phenomena of great diagnostic value. The patient in whom rupture of an intracranial aneurysm occurs is stricken with sudden headache or severe pain in the nape of the neck and may lose consciousness. There is rigidity of the neck and a mild Kernig sign. The deep reflexes are depressed. The pupils are unequal, irregular in outline and may change their size and shape from day to day. There may be hyperemia of the optic discs or even retinal hemorrhages.[31, 32] Slight fever and leukocytosis occur. The cerebrospinal fluid is bloody and successive portions of a single specimen are uniform in color. The blood in the cerebrospinal fluid does not clot; the erythrocytes settle out, leaving a clear supernatant fluid.

For a ruptured intracranial aneurysm, absolute rest is the safest therapeutic measure. Spinal puncture, other than the diagnostic one, is contraindicated. Cure of the unruptured or non-leaking aneurysm has been attempted, at times with success, by ligation of the carotid artery.[12, 13, 14, 33] In untreated cases, the duration of symptoms varies remarkably between a few minutes and many years.

The following report illustrates the progress of a large aneurysm of the internal carotid artery which gave symptoms for at least 10 years.

Case Report

M. C., a 24-year-old white girl, was admitted to the service of Dr. Irving J. Sands at The Jewish Hospital of Brooklyn, on November 29, 1936, because of headache and vomiting of three days' duration and generalized convulsions one hour before admission. The convulsive movements were uncontrollable and were most prominent in the right upper extremity. She was stuporous, her temperature was

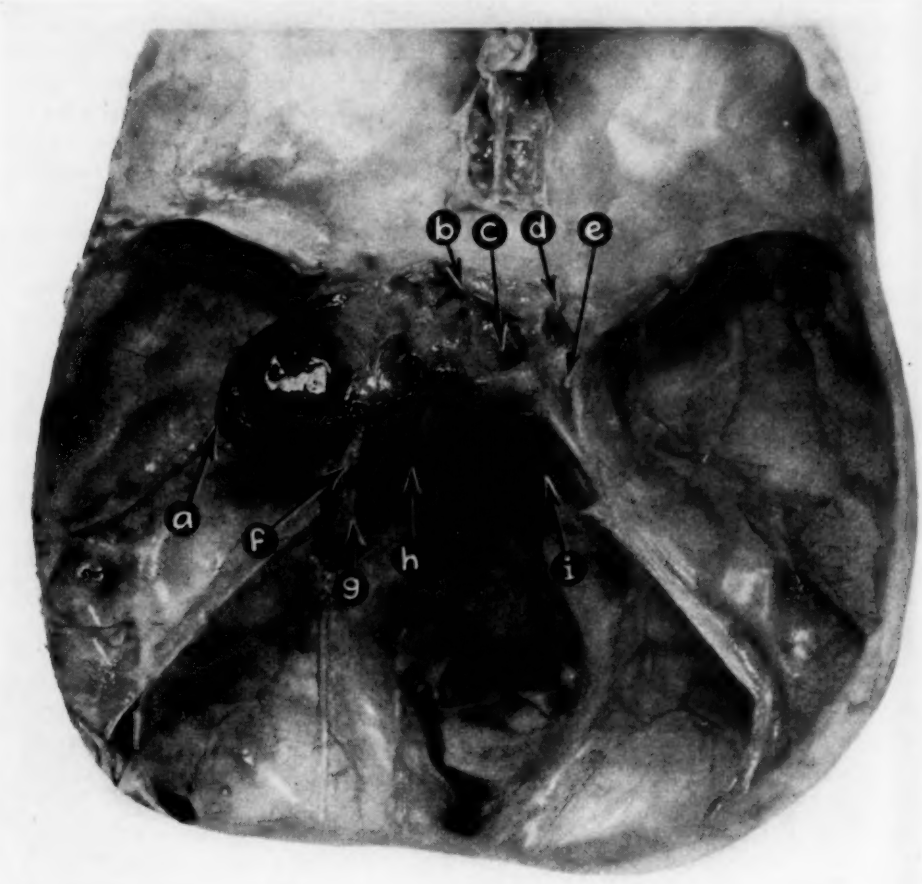
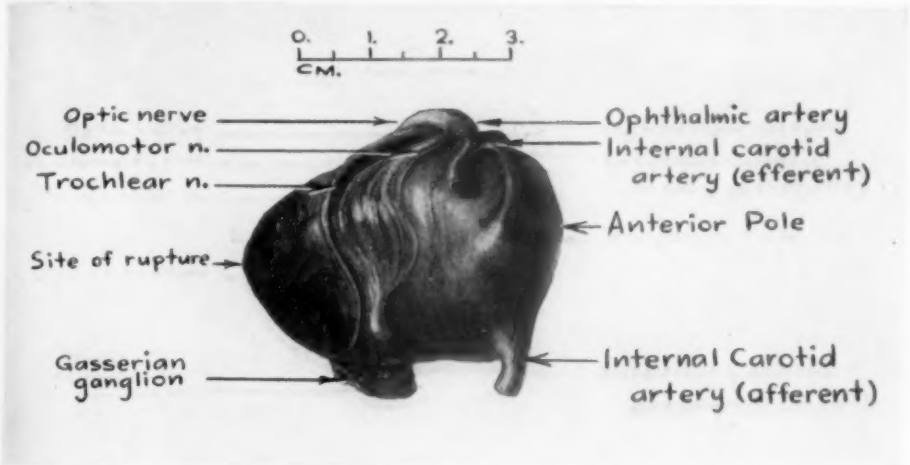


Fig. 1. Aneurysm of left internal carotid artery in floor of cranial cavity, viewed from above; *a*. ruptured posterior pole covered with clotted blood; *b*. anterior clinoid process displaced by anterior pole of aneurysm; *c*. hypophysis cerebri; *d*. right internal carotid artery; *e*. right oculomotor nerve; *f*. left oculomotor nerve; *g*. left trigeminal nerve; *h*. left abducent nerve; *i*. right abducent nerve.

101.4° F., her pulse 84, and respirations 20 per minute. The pupils were fixed, the left much larger than the right. The vessels in the fundus of the left eye were engorged, especially at the center of the disc, and there was slight haziness of the disc margin. There was no rigidity of the neck. The superficial abdominal reflexes were not elicited; all the deep reflexes were present and there was a right Babinski reflex. The cerebrospinal fluid was pink and under a pressure of 170 mm. of water. Three c.c. of fluid were removed. Shortly thereafter the patient became cyanotic. Her

pulse was weak and 150 per minute. Respirations were 10 per minute and the blood pressure was 108 mm. of mercury, systolic, and 54 mm., diastolic. Her stupor deepened and she died about 35 minutes after admission. The diagnosis made was ruptured aneurysm of the left posterior communicating artery of the circle of Willis.

Subsequently, the following information was obtained from Dr. Israel Strauss of Manhattan. The patient's birth had been normal. In her infancy a slight flattening of the left side of her face was noticed. When her teeth erupted, those on



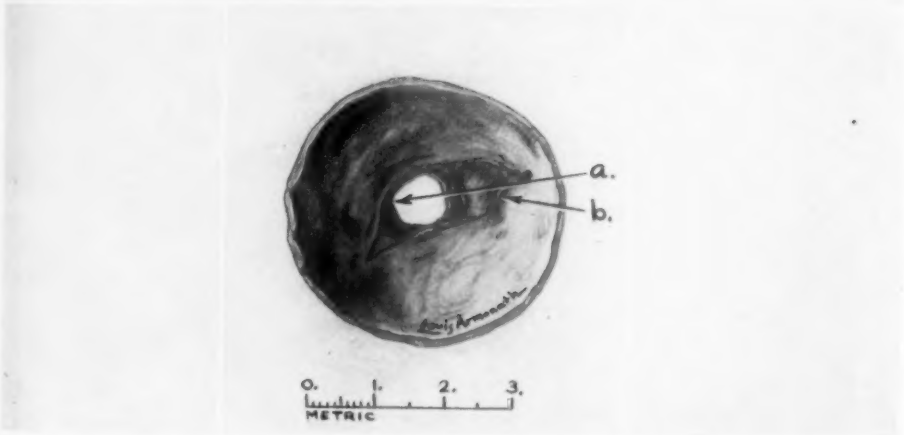


FIG. 2 (Above). Aneurysm of internal carotid artery, medial aspect.

FIG. 3 (Below). Aneurysm of internal carotid artery, posterior pole viewed from within; *a.* edge of laceration in sheath of dura mater; *b.* edge of laceration in aneurysmal wall proper.

the left side did not develop as well as those on the right. On exposure to cold, the left side of her face, particularly the chin, became blue. She had no serious illness until 1925, when, at the age of 13, she was in bed with the 'grippe' for two or three weeks. Following this she had occasional attacks of petit mal, consisting of momentary dizziness and clouded consciousness, with no sensation of falling and no headache. About one year later she began to see double. This always occurred when she looked to the left and sometimes when she looked straight ahead. She had no

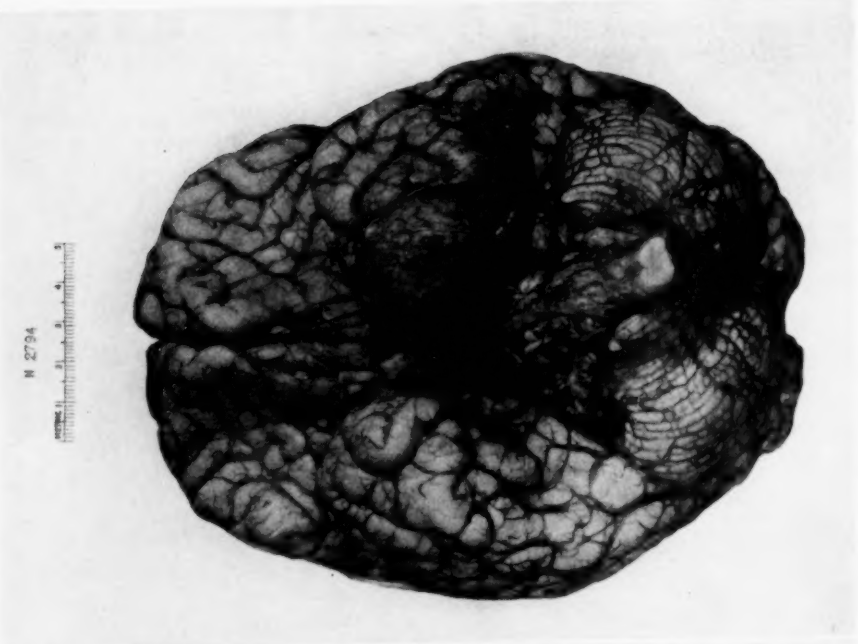


FIG. 5. Brain, ventral view, with aneurysm replaced in concavity in left temporal lobe. The black thread passes through the stump of the left internal carotid artery proximal to the aneurysm. The inaccurate fit is due to shrinkage of the brain during fixation.

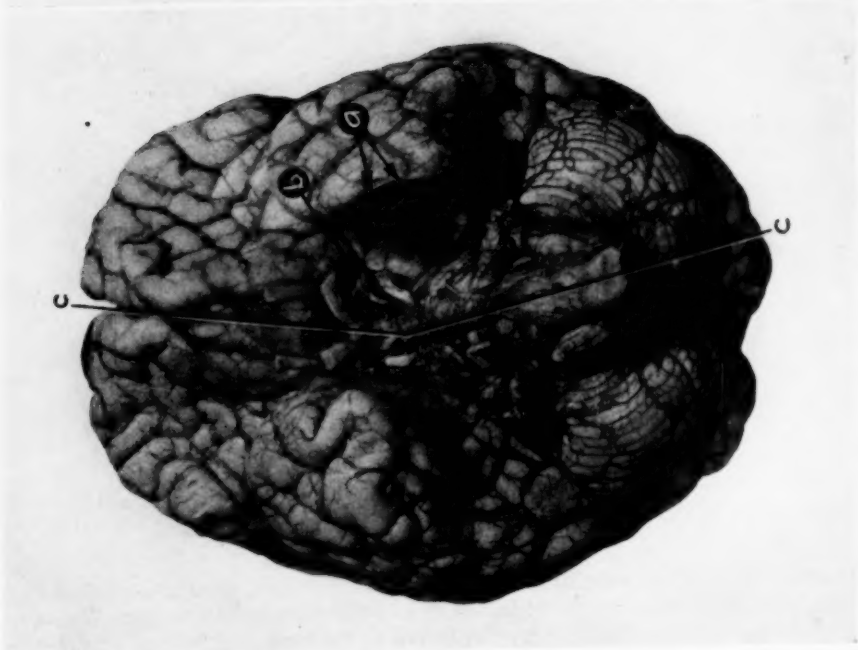


FIG. 4. Brain, ventral view, after fixation; *a*. sharp rim of concavity in left temporal lobe; *b*. left middle cerebral artery, medial to concavity; *c*. angulated median axis of cerebrum and brain stem.

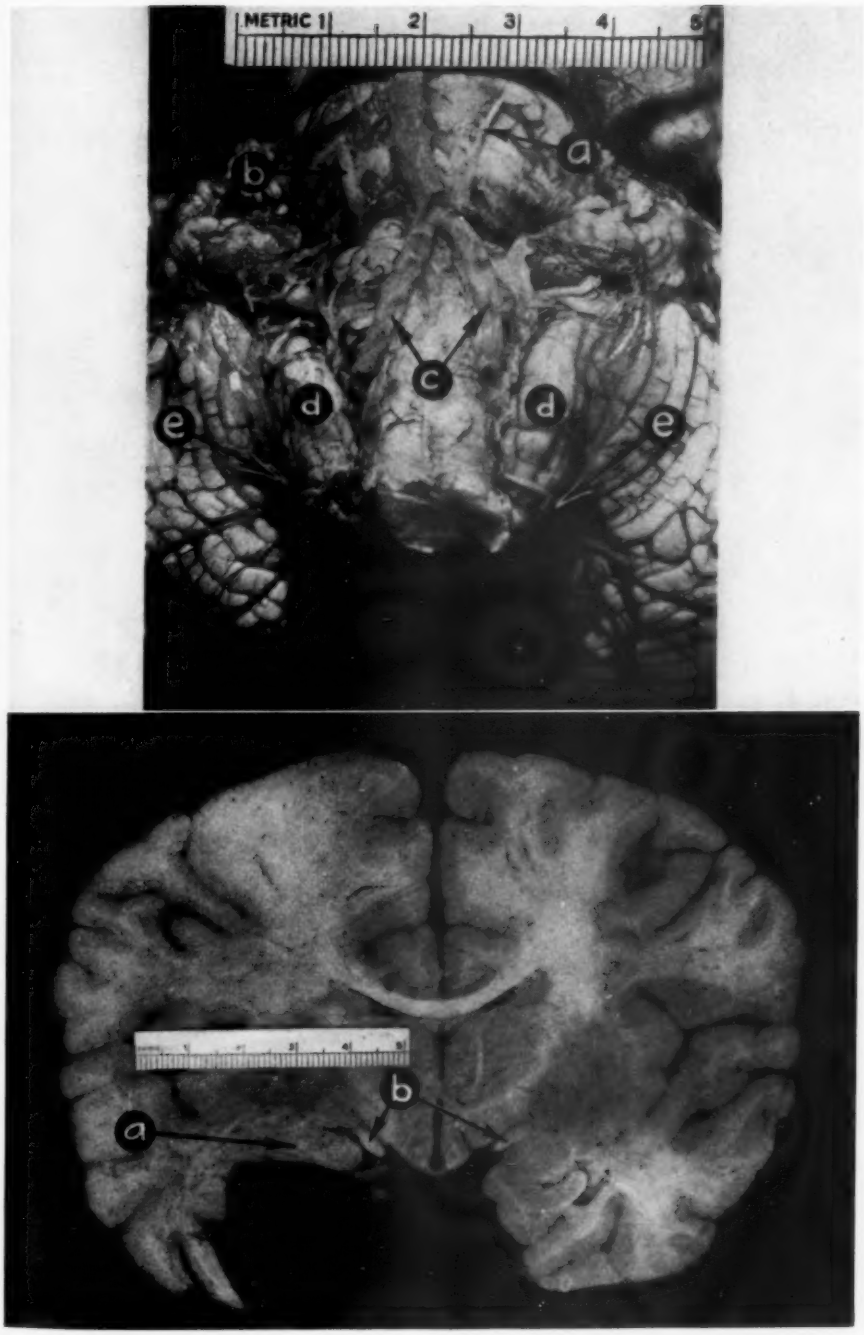
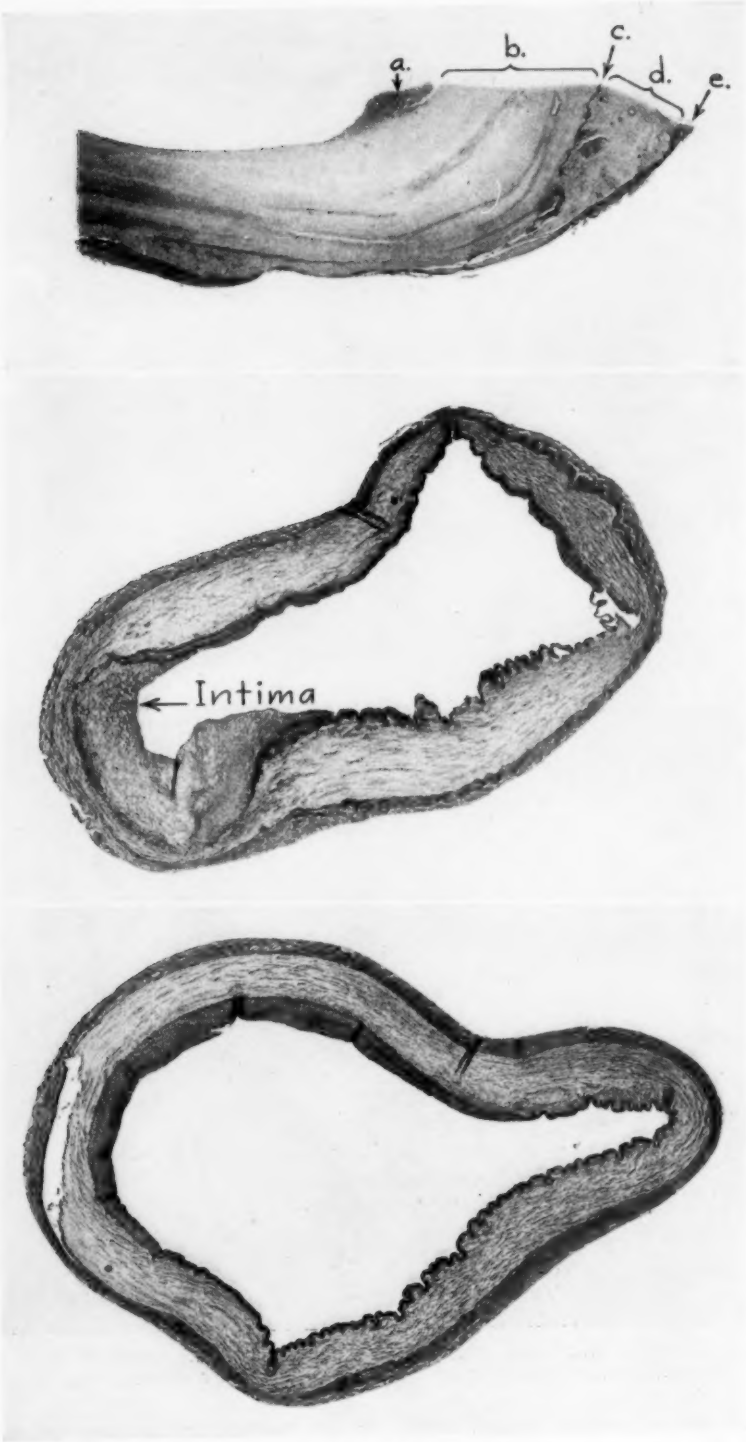


FIG. 6 (Above). Hindbrain, ventral view; *a.* left abducent nerve; *b.* right abducent nerve; *c.* vertebral arteries joining to form basilar artery; *d.d.* cerebellar tonsils exaggerated by pressure grooves, *e.e.*

FIG. 7 (Below). Brain, coronal section through concavity in left temporal lobe, viewed from behind; *a.* distorted pattern of compressed gray and white matter; *b.* optic tracts in oblique section.



FIGS. 8, 9A, 9B.

difficulty in reading at close range, but at the cinema, in order to avoid the double images, she sat in the left side of the theatre and kept her eyes turned to the right. Although worried by her attacks of mental confusion, she displayed no bad habits and made satisfactory progress in school.

In November 1926, roentgenograms of her skull were reported negative. On July 5, 1927, weakness of the external rectus muscle of the left eye was detected. The other eye muscles and the optic discs were normal. Two days later, Dr. Strauss affirmed the appearance of atrophy of the left side of her face. The seizures of petit mal ended after the year 1927. During the summer of 1928, the eye difficulty became worse and she saw double not only when looking to the left and forward, but also when looking slightly to the right. In November 1928, examination of her eyes disclosed complete paralysis of the left external rectus muscle and roentgenograms of her skull showed irregularity and narrowing of the left sphenoidal fissure.

She had no further complaints during the next few years and was able to maintain employment as bookkeeper and stenographer. In April 1931, Dr. Strauss noted that the right superficial abdominal reflexes were less active, and the right patellar reflex was more active than the left. Some time in 1933 the patient complained of seeing spots before the eyes, more before the left than the right. Otherwise she had no new symptoms, until November 26, 1936, when the headache and vomiting of her brief terminal illness began.

Necropsy. Permission for necropsy was restricted to examination of the head. The body was 165 cm. tall and weighed approximately 50 kg. Both eyes were deviated to the right; the pupils were equal, each being 0.8 cm. in diameter. On the left side of the chin there was a faint purple area measuring 2.5 by 1 cm. Two lower left teeth were missing. The head was well shaped and the calvarium was of the usual thickness. There was freshly clotted blood beneath the dura mater in the left temporo-parietal region, under the left temporal lobe of the brain and about the left cerebellar hemisphere. The inferior portion of the left temporal lobe (figures 4 and 5) was compressed by, and molded over an aneurysm arising from the left internal carotid artery just above the foramen lacerum. A deep pressure groove was noted on the under surface of the cerebellum (figure 6).

The aneurysm (figure 1) formed an oval sac enveloped in dura mater, 4.5 cm. long, 3.5 cm. from side to side and 4 cm. from top to bottom. It rested in a depression in the left middle fossa of the skull, with its long axis parallel to the ridge of the left petrous bone, and formed a broad concavity in that bone, in the left side of the body of the sphenoid bone and in the left side of the hypophysis cerebri. The left clinoid processes were spread apart and elevated by the anterior pole of the aneurysm.

The left internal carotid artery opened into the aneurysm near the junction of the anterior and middle thirds of its inferior surface and emerged from its medial aspect near the anterior pole (figure 2). At these two points the lumen of the artery was continuous with the cavity of the aneurysm. The efferent portion of the artery lay against the wall of the aneurysm and, after curving upward and backward for a distance of 2.5 cm., became the left middle cerebral artery. The left ophthalmic artery and the optic nerve were separated from the upper surface of the aneurysm

FIG. 8 (Above). Wall of aneurysm, anterior pole; *a.* clotted blood; *b.* thickened intima; *c.* interrupted internal elastica; *d.* rapidly narrowing media; *e.* adventitia. Combined van Gieson and Weigert stain, magnified × 50.

FIG. 9A (Center). Left internal carotid artery, just proximal to the aneurysm. In one segment the intima is widened, the internal elastica interrupted and the media almost obliterated. Combined van Gieson and Weigert stain, magnified × 50.

FIG. 9B (Below). Right internal carotid artery, at a level corresponding to that in A. The intima in a large segment is wide and contains numerous elastic laminae; the media is unchanged. Combined van Gieson and Weigert stain, magnified × 50.

by the thin posterior root of the lesser wing of the sphenoid bone. The oculomotor and trochlear nerves were compressed and spread out between the superior surface of the aneurysm and the overlying dura mater. The trigeminal ganglion, with its branches, was flattened between the inferior surface of the aneurysm and the floor of the middle cranial fossa.

There was no trace of the left abducent nerve, except for a stump one cm. long, at its origin from the inferior border of the pons Varolii. This portion of the nerve was 0.1 cm. thick and the corresponding portion of the uninvolved right abducent nerve was 0.2 cm. thick (figure 6). The left facial nerve was not implicated by the aneurysm.

The aneurysmal sac was almost entirely filled with dark red clotted blood, easily separated from the wall. The intimal surface of the sac was smooth, gray and con-

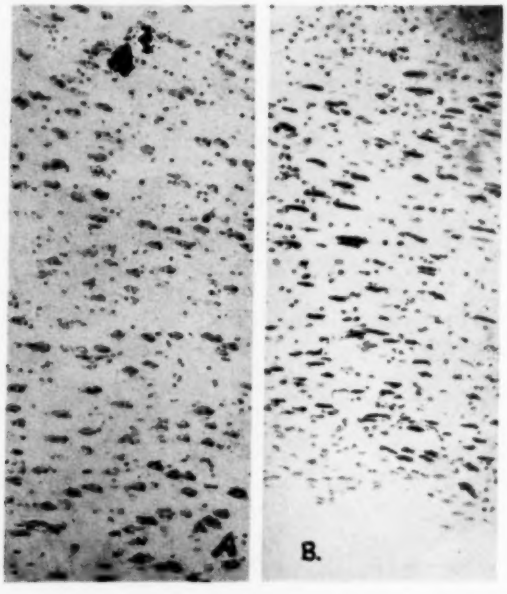


FIG. 10A (Left). Cerebral cortex, left temporal lobe. The neurons are compressed and the cellular detail obliterated. Nissl stain, magnified × 150.

FIG. 10B (Right). Cerebral cortex, right temporal lobe. The neurons are not distorted and the cellular detail is preserved. Nissl stain, magnified × 150.

tained occasional irregular yellow areas up to 0.3 cm. in diameter. The thickness of the wall varied from 0.12 cm. at the anterior pole, to tissue paper thin in nearby areas. A ragged laceration 3.5 cm. long and 0.7 cm. wide extended across the posterior pole (figure 3). In the overlying dura mater there was a circular opening 0.5 cm. in diameter, through which protruded strands of clotted blood.

The calibre of the left internal carotid artery, proximal and distal to the aneurysm, was nearly the same as that of the uninvolved right internal carotid. The other members of the circle of Willis were not unusual. The exact relationship of the left cavernous sinus to the aneurysm was not determined.

Microscopically, the wall of the aneurysm was composed of a broad intimal layer of hyalinized fibrous connective tissue, with, here and there, remnants of medial smooth muscle and elastic fibers (figure 8). Near the laceration in the posterior pole, the connective tissue fibers were frayed and spread apart by extravasated blood.

In a transverse section through the left internal carotid artery proximal to the aneurysm (figure 9A), a segment of intima, about one-sixth the circumference of the vessel, was markedly widened and the underlying media narrowed, in one area almost to obliteration. The widened intima consisted of a broad inner zone of fine connective tissue fibrils with few nuclei and a narrow outer zone with many, closely packed nuclei and some elastic fibers. Irregular clear spaces and occasional large cells with foamy or vacuolated cytoplasm and a small dark nucleus, were present in places. In a corresponding section through the right internal carotid artery (figure 9B) the intima for one half the circumference of the vessel was thickened by an increase of both collagenous and elastic fibers; the media was not altered. Preparations from other intracranial arteries were not unusual.

No distinct histologic changes were noted in myelin stains of any of the cranial nerves. In a Spielmeyer myelin stain of the pons Varolii, there was a slightly paler area in the reticular formation near the sixth nerve nucleus. In a preparation from the compressed portion of the left temporal lobe (figure 10A) the neurons were close together, narrowed, elongated and deep staining, with no distinction between the cytoplasm and nucleus.

Comment

In this young woman, the unheralded onset of headache and vomiting, followed in a few days by convulsions and stupor and attended by pupillary changes, indicated the presence of an expanding intracranial lesion. That it was a left sided lesion was suggested by the right Babinski reflex and the vascular engorgement of the left fundus. That it was a ruptured intracranial blood vessel was evidenced by the bloody spinal fluid under increased pressure.

One can merely speculate on the connection of the aneurysm's origin with the observations made during the patient's infancy, or with the attack of "grippe" when she was 13 years old. On the other hand, the petit mal and the diplopia point decisively to the presence of a sizeable vascular dilatation, or of a defect permitting its formation, 10 or 11 years before the patient's demise. Cessation of the attacks of mental confusion was probably due to accommodation of the brain to its early displacement or distortion. The spots before the eyes may have been caused by either a disturbance in circulation through the cavernous sinus or compromise of some fibers of the optic tracts where they pass through the white matter of the compressed left temporal lobe (figures 1, 2 and 9A). The latter is more likely, since the spots appeared before both eyes.

This aneurysm is classed as congenital because of its early onset and the absence of clinical arteriosclerosis, syphilis, endocarditis or trauma. Nevertheless, the possibility cannot be gainsaid that its origin is based upon a lesion of the artery occurring at the time of the grip-like infection. What additional information a complete necropsy would have supplied cannot be known. The structural alterations in the walls of the intracranial arteries were not specific. Those changes in the arterial wall close to the aneurysm create suspicion of a medial defect as the initial weakness, followed by the fatty and fibrous transformation of the intima.

Summary

A case of intracranial arterial aneurysm is presented together with a general discussion of the subject. The aneurysm, affecting the carotid artery of a 24-

year-old woman, had given symptoms for more than 10 years and had grown to unusual size. Its origin was probably congenital.

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POLYRADICULONEURITIS, WITH REPORT OF CASE*

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The condition, variously known as infectious neuronitis, polyradiculoneuritis, polyneuritis, myeloradiculitis and polyneuritis pseudomyopathic, undoubtedly occurs more frequently than it is recognized. It appears to have been first discussed by Osler in 1892 under the designation of acute afebrile polyneuritis. Mills mentioned it in 1898 at the time the neuron theory was adopted. In 1916 Patrick noted the occurrence of facial diplegia in the syndrome of polyneuritis. In 1927 Viets mentioned the high total protein content of the spinal fluid as a diagnostic factor.[1] There has been considerable discussion at times regarding its terminology, especially directed against the use of the term neuronitis, as misleading. Cobb and Coggeshall[2] in 1934 discussed the principal causes of neuritis at some length. They divided the generalized polyneuritides into four classes: those cases due to virus, bacterio-toxic, deficiency or metabolic, and chemical causes. Included in the virus class were such conditions as measles, smallpox, chickenpox, parotitis, herpes, acute febrile polyneuritis, acute infective polyneuritis, Landry's disease, poliomyelitis, encephalomyelitis, lethargic encephalitis, erythroedema, and acute rabic myelitis. The condition under discussion may be identified as an acute infectious generalized polyneuritis. Certain distinguishing clinical and laboratory characteristics, to be mentioned later, indicate that it is a distinct clinical entity.

Some clinical features of the condition bear considerable resemblance to anterior poliomyelitis, polyneuritis due to diphtheria or even to some of the myopathies. Some of the remarkable recoveries described as having occurred following the above conditions suggest rather polyradiculoneuritis as the condition actually present. We have seen one case of progressive muscular dystrophy (pseudo-hypertrophic muscular dystrophy) in an adult, in which, for about two years some observers had held that the condition was due to infectious neuronitis. The persistent and progressive advance in the symptoms and physical findings in this case, together with the presence of marked muscular atrophy, however, proved the condition to be one of muscular dystrophy.

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The actual etiology is not definitely known. In a certain, possibly the larger number of cases, there has been an acute infection, frequently of the upper respiratory tract, present for several days to several weeks prior to the onset of the disease. Some writers mention various other factors which are noted in other forms of multiple neuritis as possible etiological factors in this condition, such as poisoning with the heavy metals, including gold, avitaminosis, alcohol, barbital, emetine and syphilis. The theory of a virus as the etiological factor finds considerable favor. While the disease may occur at any age it is more frequently present in adults. The onset may be fairly sudden, with weakness and paresthesia of the extremities, generally more marked in the lower. There is usually some disturbance of sensation but this is not marked. The muscles of the face may be involved and even the cranial nerves, although the latter are generally intact. Sphincter control is not affected as a rule. Severe pain is occasionally present, but is not noted in other cases. Ordinarily there is no fever. The characteristic features are the rather rapid and widespread involvement of all the extremities in a flaccid paralysis, of varying degrees of severity, with little in the way of other clinical or laboratory findings to account for the condition. The characteristic laboratory finding is an increase in the total protein of the spinal fluid with a normal or but slightly elevated cell count, a slight increase in globulin and a colloidal gold of the meningitic type, any increase of cells being of the lymphocytic variety.

The paralysis tends to increase steadily and may be so extensive as to render the patient entirely helpless. The deep reflexes are diminished or absent, no fibrillation is noted in the muscles and no atrophy other than may arise late in the disease as a result of disuse. There is frequently some muscular pain and tenderness. Choking of the optic discs occurs in some cases. Of 20 cases reported by Gilpin, Moersch and Kernohan [1] the total protein of the spinal fluid varied from 100 to 800 milligrams per 100 c.c., increasing steadily during the early period of the disease, as did the cells, which averaged 12 lymphocytes per 100 c.c. of fluid. The colloidal gold in their cases was mid-zone in 50 per cent and first zone in 25 per cent; the sugar and chloride of the spinal fluid were normal.

Abadie, Bergouignan and Verger [3] noted a slow onset in some cases and remarked that it was not unusual to note fibrillary tremors in the muscles after light percussion. They found also that marked pain may be present throughout the extremities, paroxysmal in severity, but the pain later disappears, leaving only tenderness to pressure over the muscles and perhaps the peripheral nerves. A case which these authors reported showed a marked intensity, with extension to all the masses of skeletal muscles, of fibrillary tremors, which were incessant; they believed that these tremors were evidence that the infectious process was not limited to the peripheral nerves; that it was a question not of a pure polyneuritis, but a diffuse infectious celluloneuritis.

Pathologically, the affected peripheral nerves show degenerative changes without any evidence of an inflammatory reaction. There is also involvement of the dorsal root ganglia, with lymphocytic infiltration. The pathologic changes may extend to the spinal cord and to the brain; they are patchy in distribution.

While the clinical picture is generally quite uniform the disease may be mild and of short duration, long and severe or fatal. H. D. McIntyre [4] separates the cases into four groups from a clinical standpoint:

(1) Group with rapid onset, with rapid recovery, usually with some evidence of seventh nerve paralysis.
(2) Group with steady downward progress with early death.
(3) Group with long drawn out course, with incomplete recovery.
(4) Group with long drawn out course, terminating in death, usually from heart failure, bulbar or respiratory paralysis.

The diagnosis is based on the history of the preceding illness and a latent period of well being; then the development of the polyneuritis. There may be involvement of the cranial nerves with facial palsy, or choking of the discs. The increase of total protein in the spinal fluid, with but slight change in the cell count, is the diagnostic laboratory finding. This finding is possibly not always present, especially at the time the patient is seen as it may be transitory and its absence late in the disease, if the patient is first seen then, would have little diagnostic significance, either negatively or affirmatively. The electrical reaction of the affected muscles is always that of degeneration, more frequently incomplete, the changes being most marked in the muscles of the extremities, scapular and pelvic girdles and anterior abdominal wall.[3] The reaction may appear also in muscles which are clinically not affected.

The differential diagnosis includes anterior poliomyelitis, Landry's paralysis, diphtheritic paralysis and certain of the myopathies. In anterior poliomyelitis the markedly rapid onset and progression, with fever, leukocytosis, with polymorphonuclear increase and the pleocytosis of the spinal fluid are indicative of this disease. In Landry's paralysis the rapid onset and progression, generally from the lower extremities upward, with absence of increase in the total protein of the spinal fluid and usually an early fatal termination, should suffice for differentiation. In the myopathies, aside from the hereditary family character of the affection, the onset is one of marked slowness, without any initial infectious episode and while the muscle reflexes are abolished tendon reflexes do not disappear until late; also there are no sensory disturbances. The cerebrospinal fluid is normal and the electrical reactions are not those of degeneration. In infectious polyradiculoneuritis the changes in the motor cells of the spinal cord, in the nerve roots and posterior ganglion cells, and the secondary rôle played by peripheral lesions differentiate the condition from ordinary peripheral neuritis. According to McIntyre the albumino-cytologic dissociation in the spinal fluid differentiates infectious neuronitis from the toxic neuritides, in which the globulin is never so greatly increased while toxic neuritis, such as that due to alcohol and arsenic, shows a more peripheral character of the neuritis and lacks the albumino-cytologic dissociation. He warns against overlooking a previous diphtheritic infection as an etiological factor.

While recovery is the general outcome in this disease, death in the more severe cases, especially from respiratory failure, is not infrequent. The acute stage is generally from one to three months in duration, the entire course of the illness lasting from a few months to two and one-half years. Usually recovery is complete, there being no residuals of any nature; this is in contra-distinction to the true myopathies where permanent damage is to be expected.

The treatment is entirely symptomatic; complete bed rest is of the first importance; attention to elimination; a high vitamin diet, with especial attention to vitamin B_1; assurance of an adequate fluid intake, and sedation as required

for the pain, are obvious measures. Later in the disease gentle massage, baking and other mild physiotherapy measures may assist in a more rapid return to normal of the affected muscle groups. Electricity, per se, as a form of treatment has no place and may possibly do harm in the early stages. Good nursing and attention to the eyes and dental hygiene should not be neglected. Because of lacrimation, drooling from inability to swallow well and the patient's inability in certain cases to help himself in any way, a special attendant is required.

Case Report

An interesting case of the above condition, occurring in a white male, aged 19 years, and showing extensive involvement, including the cranial nerves, was admitted to the hospital at Fort Sam Houston, Texas, on October 29, 1937. The family history and previous personal history were unimportant. The patient denied the use of alcohol (except occasionally beer) and tobacco. He denied all forms of venereal disease. The onset of the present illness had been noted one week previously, in the form of progressive weakness in both legs. There was no history of any previous acute infection or of any other illness. The patient stated that the first symptom noted was numbness and coldness of the toes of both feet; about 24 hours later he noticed difficulty in stooping to lift a small package from the ground and he had to rest at frequent intervals while on duty as a night watchman. On the second day following he noted pain in the right temple, extending across the forehead. There was no dizziness. Later that same day there was some difficulty in swallowing. He reported sick and was placed in bed; his temperature was normal. On the following day there was considerable difficulty in swallowing; his legs had been getting progressively weaker and at this time he was unable to lift them from the bed. After three days in the CCC Infirmary he noticed that his arms had also become weak and that there was numbness in his finger tips, his right arm being weaker than the left. There was severe pain in the temples almost constantly at this time. On the fifth day of his illness, and while still at the Infirmary, he fell to the floor and could scarcely arise; he could stand on his feet but could not walk. Upon his arrival at the hospital at Fort Sam Houston, Texas, seven days after the onset of his illness, he was unable to sit up because of muscular weakness and there was a flaccid paralysis of both lower extremities. There was also considerable weakness of the muscles of both arms and of the face, he had marked difficulty in swallowing and could scarcely raise his head from the pillow.

Physical examination showed a well developed young adult male. He had an anxious, worried facies; was well nourished. Vision, hearing and smell were normal. The fauces and pharynx were reddened and granular; the tonsils also were reddened and engorged. The pulse was full and a little rapid. The heart and lungs were negative on examination. Blood pressure 124 systolic and 78 diastolic, right arm, in millimeters mercury, the patient being recumbent. External genitalia normal. Bones and joints normal. The pupils were equal, regular in outline and reacted but sluggishly to light. The eyes moved freely in all directions; there was no diplopia and no definite ptosis noted at this time. The left seventh cranial nerve showed marked weakness and the left eyelid did not close completely. The tongue deviated to the right. The pharyngeal muscles showed weakness, liquids regurgitating through the nose when he attempted to swallow. All of the deep reflexes were markedly decreased, and the cremasteric and abdominal reflexes were absent bilaterally. The patient complained of paresthesia in the left arm and leg; tactile acuity was diminished in the right arm and leg. The joint and vibratory senses were normal; there was no clonus or Babinski, no muscular fibrillation and no disdiodokokinesis. He complained of pain in the right side of the skull, anteriorly, present for the past week. Although obviously acutely ill the temperature was normal. He was unable to move

the lower extremities and there was marked weakness in both upper extremities, so much so that he was unable to care for himself in any way. He was mentally clear.

Soon after admission to the hospital he developed bilateral facial paralysis, with increased weakness of the pharyngeal muscles. Tube feeding was required for a period of more than two weeks. There was considerable respiratory difficulty, due to involvement of the diaphragm and of the accessory muscles of respiration. He had increased lacrimation, bilaterally, and inability to close either eye, he drooled considerably, there being apparently some increased secretion, together with inability to swallow well. His temperature remained normal throughout his illness and he was always clear mentally.

The electrocardiogram showed sino-auricular block with ventricular escape. The cardiac rate during the first few weeks of his hospitalization ranged from 98 to 144 per minute. Roentgen-ray of the chest showed the heart and lungs to be negative.

The paralysis of the upper extremities soon became more marked, especially in the proximal groups of muscles, the patient being unable to elevate the arms at the shoulders, although there was some power of flexion at the elbows. Electrical tests of the involved muscles failed to demonstrate any reaction of degeneration. The muscles of the upper extremities responded normally to the faradic current. All the muscles of the lower extremities responded to the faradic current, except the *peroneus brevis* and *extensor digitorum brevis* but some of the responses were weak, as in the *abductor longus,* left; *vastus externus,* left; *extensor communis digitorum,* left; *extensor hallucis,* left; *rectus femoris,* right; *peroneus longus,* right; *tibialis anticus,* right, and *extensor hallucis,* right. All the muscles which were weak on faradic responses responded normally to the galvanic current.

The eyes, including the lens, media and fundi, were normal, the discs being clearly defined and showing no elevation.

The white blood count on the day following admission showed 7,900 cells with 72 per cent neutrophiles; on November 13, 10,600 cells with 82 per cent neutrophiles. The red blood cells and hemoglobin were normal. The blood Wassermann and Kahn were negative. Repeated urine specimens were negative with one exception when albumin, a few white blood cells and a few finely granular casts were noted. A spinal fluid specimen taken at the time of his admission to hospital was practically negative; there were 5 cells, a very slight trace of globulin and the colloidal gold was 1 2 2 2 2 2 2 1 0 0; the Wassermann was plus minus in the 1 c.c. specimen, negative in the others. The sugar content was 73.5 milligrams per 100 c.c.; the pressure was 5 millimeters of mercury. Seven specimens of spinal fluid taken subsequently over a period of six weeks showed about the same findings, except that the Wassermann was always entirely negative; the highest cell count noted was 7 cells; the globulin was always slightly positive; the pressure varied from 5 to 6 millimeters of mercury; the sugar content was 67.1, 68.9, 61.7 and 63.3 per 100 c.c. fluid. The colloidal gold was 4 4 4 4 2 2 1 1 0 0; 4 4 4 4 4 4 3 2 2 0 0; 2 4 4 2 2 2 2 1 1 0 0 and 0 0 1 2 1 0 0 0 0 0. The culture of the spinal fluid was repeatedly negative. The total protein content of the spinal fluid, however, showed the alteration generally considered as diagnostic of polyradiculoneuritis, that is an increase which rose from 18.4 milligrams per 100 c.c. to 122 milligrams, the height of the curve being on November 26. The curve then gradually decreased to normal (15 to 45 milligrams considered normal).

The blood chemistry (sugar, urea nitrogen, CO_2) soon after admission showed a slight increase in urea and a slight decrease in the CO_2 combining power. The throat culture at the time of admission showed a heavy infection with *Streptococcus viridans* and some Vincent's organisms, later hemolytic streptococci were found in considerable number in the throat smear.

The patient was discharged on March 22, 1938, approximately five months after admission. At that time he was ambulant, capable of taking moderate exercise, the difficulty in swallowing and tachycardia had entirely disappeared. His muscular strength had practically returned to normal, yet there was still some weakness and lack of endurance. Reaction to the faradic current was practically normal. Patient stated he felt quite well and recovery was apparently complete.

This case was a rather unusual one in that the vagus, bilateral facial, and pharyngeal nerves were involved, in addition to the generalized spinal involvement. This patient's electrocardiogram had returned to normal prior to his discharge. The fact that the total protein in the spinal fluid was not as much increased as is frequently seen and the relatively short period of illness would indicate a pathologic process of moderate intensity in spite of the massive involvement. We were unable to locate any reference in literature to vagus involvement in this condition. The findings as a whole were quite typical:

a. The extreme involvement in the cerebral and spinal nerves, with minimal sensory changes.
b. The afebrile course.
c. Normal blood picture.
d. Normal cerebrospinal fluid, except for the increased total protein.
e. The lack of atrophy in the involved muscles.
f. Complete recovery.

Although the patient denied any previous illness of any kind, a focus of infection in the throat as a possible etiological factor is to be considered, in view of the finding of streptococci in considerable numbers at the time of his admission to the hospital.

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EDITORIAL

SULFANILAMIDE AND THE BLOOD

It is extremely unfortunate that the administration of sulfanilamide, which has proved so valuable in the treatment of certain bacterial infections, should give rise to such a variety of toxic manifestations in human beings. The most serious of the toxic effects that have been observed to date are those upon the peripheral blood and the hemopoietic system, to wit acute hemolytic anemia and granulocytopenia. The cyanosis so commonly noted during the course of sulfanilamide therapy may at times be due to methemoglobinemia, but in most instances it is apparently caused by the formation of some colored compound which is of no particular clinical significance.

Some time before Harvey and Janeway [1] published their initial report on three cases of acute hemolytic anemia following the use of sulfanilamide, it had been postulated by hematologists that the drug might be expected to produce agranulocytosis and other forms of blood dyscrasia on the basis of its chemical structure involving the benzamine linkage. Since the original communication of Harvey and Janeway, a number of cases of acute hemolytic anemia have been recorded both in this country and abroad. In his recent review of a series of 522 patients treated with sulfanilamide Wood [2] found that acute hemolytic anemia developed in 21 or 4 per cent. It is of interest that the incidence among the 144 children included in the series was 8.3 per cent in contrast to 2.4 per cent among the 378 adults.

This acute hemolytic anemia following sulfanilamide presents a well-defined clinical picture, characterized by fever, malaise, jaundice, a rapid fall in the erythrocyte count and the hemoglobin level, a moderate to marked leukocytosis, marked reticulocytosis, hyperbilirubinemia, urobilinuria, and in certain instances porphyrinuria. In a few cases evidences of hemoglobinuria and hemoglobinemia have been noted. Signs of hemolysis are usually recognizable within 24 to 72 hours after the administration of the drug has been started, and the maximal anemia generally develops within three days after the hemolytic process is initiated. The hemoglobin level may drop from a value of 90–100 per cent to as low as 20–30 per cent in an amazingly short period of time. The leukocyte count may rise to a level of 60,000 to 100,000 white blood cells per cubic millimeter. The blood smear shows signs of sudden stimulation of the bone-marrow with the outpouring of many immature cells of the myeloid series in addition to large numbers of nucleated red cells and reticulocytes. The fragility of the erythrocytes in saline solutions has been normal in the cases reported so far. The clinical features and blood changes in this type of hemolytic anemia are

[1] HARVEY, A. M., and JANEWAY, C. A.: The development of acute hemolytic anemia during the administration of sulfanilamide (para-aminobenzene-sulfonamide), Jr. Am. Med. Assoc., (July 3), 1937, cix, 12–16.

[2] WOOD, W. B., JR.: Anemia following sulfanilamide therapy, Jr. Am. Med. Assoc. (in press).

very similar to those found in two other forms of acute hemolytic anemia, the acute "idiopathic" hemolytic anemia of Lederer and the hemolytic anemia of favism. The latter is very rare in this country but quite common in southern Italy. It is apparently caused by a toxic substance present in the fava bean to which certain individuals, frequently several members of the same family, become in some way hypersensitive. Ingestion of the bean is followed by an acute febrile illness accompanied by jaundice and severe anemia.

The mechanism of the production of hemolytic anemia by sulfanilamide is not understood. There is no evidence that any one type of infection predisposes an individual toward this form of anemia. The size of the dose does not appear to be of much importance, for many individuals tolerate large doses of the drug over long periods without developing anemia. Furthermore, there was no correlation between the level of sulfanilamide in the blood and the development of acute anemia in Wood's series of cases. Individual idiosyncrasy undoubtedly is a major factor, for a very small percentage of patients treated develop the acute anemia and, as Wood has shown, once an individual has developed an acute hemolytic anemia the chances are very great that he will suffer a recurrence of the anemia if a second course of sulfanilamide is administered, even as long as a year after the initial course of therapy. Various theories have been propounded as to the mechanism by which hemolysis is induced. One of the most plausible of these is the suggestion that in the affected individuals a portion of the sulfanilamide may be converted in the body to a hemolytic compound. Attempts to reproduce the anemia experimentally in animals have met with failure up to the present.

Fortunately few fatalities have resulted from hemolytic anemia so far, for the hemolytic process, if recognized sufficiently early, can be halted as a rule by the immediate discontinuation of the drug, the administration of large amounts of fluid to rid the body of sulfanilamide as rapidly as possible, and one or more blood transfusions. The pathologic findings in the one fatal case that has been reported [3] were regarded as being representative of any severe acute hemolytic anemia. There was hemosiderosis of the liver, spleen, and kidneys; hyperplasia of the sternal and vertebral marrow with normal fatty femur marrow. The renal tubules contained some hemoglobin casts and the sections of the kidneys were said to resemble those from cases of black-water fever except for the absence of malarial pigment. No pathologic feature was noted which could be considered to be a specific lesion produced by sulfanilamide.

The other serious complication of sulfanilamide therapy, granulocytopenia, appears to be much less common than acute hemolytic anemia. Wood noted only one case of agranulocytic angina among the 522 patients in his series, and this patient made a prompt recovery after the medication was

[3] Wood, H.: A fatality from acute hemolytic anemia which developed during the administration of sulfanilamide, Southern Med. Jr., (June) 1938, xxxi, 646–649.

stopped. However, a number of fatal cases have been reported from widely scattered points. Kracke [4] in his excellent review of the relation of drugs to neutropenic states has collected 11 cases of granulocytopenia following the administration of sulfanilamide or one of its derivatives; nine of these cases were fatal. He has pointed out that with the dissemination of knowledge regarding the danger of granulocytopenia from aminopyrine the number of cases reported annually as due to this drug has greatly diminished, especially in Denmark where the use of aminopyrine has been curtailed by law. Kracke predicts that sulfanilamide will gradually replace aminopyrine as the foremost cause of granulocytopenia. The clinical and pathologic picture of granulocytopenia following sulfanilamide appears to be identical with that following aminopyrine. Once more it is evidently a matter of idiosyncrasy in the occasional patient. The mechanism of production of the granulocytopenia associated with maturation arrest in the bone-marrow is still a complete mystery.

It is of the utmost importance that physicians employing sulfanilamide in the treatment of the various acute infections be acquainted with the dangers inherent in the drug. In order to prevent the development of a serious hemolytic anemia or granulocytopenia it is urged that every patient receiving sulfanilamide should have a hemoglobin determination and a leukocyte count at least every second day. The urine should be frequently examined for urobilin. Unexplained fever, developing during the course of sulfanilamide therapy, should be regarded as a warning sign that some more serious toxic effect may be imminent. Obviously, proper supervision of the patient is only possible if he is under the constant care of a physician and preferably in the hospital. The new Food, Drug, and Cosmetic Act prohibits the sale of sulfanilamide to the public in "patent medicines." It would be even more desirable to make such drugs as sulfanilamide and aminopyrine available to the public only upon the prescription of a licensed physician, who would assume full responsibility of the care of the patient throughout the course of therapy.

[4] KRACKE, R. R.: Relation of drug therapy to neutropenic states, Jr. Am. Med. Assoc., (Oct. 1) 1938, cxi, 1255–1259.

REVIEWS

Chemistry of the Brain. By IRVINE H. PAGE, M.D. xvii + 444 pages; 17.5 × 26 cm. Charles C. Thomas, Springfield, Illinois. 1937. Price, $7.50.

According to the author this book was written in the belief that chemical investigation is essential to the development of psychiatry. It represents an up-to-date summary of our knowledge concerning brain constituents and their metabolism. Various chapters are devoted to the biochemistry of the sterols, phosphatides, cerebrosides, fatty acids, carbohydrates, proteins, inorganic elements and gases with particular emphasis upon the activity of these substances in the brain. Certain phases of physical, enzymatic, vitamin and comparative neurochemistry are given adequate consideration including a chapter on oxidations and reductions contributed by J. H. Quastel of the Cardiff Mental Hospital. In addition the clinical aspects of this subject have not been neglected.

Of interest and value is a short historical survey of the life and work of Thudichum and of the genesis of brain chemistry.

There are full references not only to the journal literature but to the leading books, monographs and reviews dealing with this subject. The book has an element of authority due to the fact that the author has been a frequent contributor in this field of research. It will be welcomed as an invaluable source of information to all investigators interested in the chemistry of the brain.

E. G. S.

Diseases of the Blood. By CYRUS C. STURGIS, B.S., M.D., and RAPHAEL ISAACS, A.B., A.M., M.D.; Edited by MORRIS FISHBEIN, M.D. National Medical Book Co., Inc., New York, N. Y. 1937.

This small handbook will be of considerable value to the medical student and to the general practitioner. It presents in a brief clear way the chief data relating to the principal diseases of the blood. If all that is in this book is well digested the physician will be better informed than the average of his fellows. The feat is fairly easy of accomplishment. If, however, the student or physician did not learn elsewhere more concerning the formation and the destruction of blood and the part they play in the pathology and symptomatology of blood diseases than is contained in this manual he would have little insight into the pathogenesis of blood diseases. The reviewer feels that the monograph produced by Dr. Sturgis and Dr. Isaacs is a very valuable brief summary furnishing an easy method for brief review of the clinical aspects of blood diseases. A few more references would add to its value.

M. C. P.

Martini's Principles and Practice of Physical Diagnosis. Edited by ROBERT F. LOEB, M.D. 213 pages; 13 × 19.5 cm. J. B. Lippincott, Philadelphia. 1938. Price, $2.00.

This small volume covers the entire field of the principles and the practice of physical diagnosis. The preface to the first edition points out that only the important "physical signs" are included and that many signs, while still in usage, have been omitted because of the development of more accurate and indispensable aids to diagnosis. The fulfillment of this intent should then lead to simplicity and clarity, and if the volume fails in these scores it is not because of the lack of content, but rather because of the arrangement of the material. The student or the beginner in the study of physical diagnosis will be hard put—in the reviewer's opinion—to gain a clear

concept of the principles underlying the physical diagnosis of the respiratory system from study of this work. Of more value to the beginner will be the sections on the circulatory system and the abdomen. These sections are clearly arranged and discussed and are the more valuable parts of Martini's work.

The first section of the book confines itself to the observation of the patient and here the author has stressed many important details. Included in the first section are some notes on the subject of acoustic diagnosis; this addition seems aside from the general purpose of the book. The discussion of the principles of palpation, percussion and auscultation is not as clear as might be desired.

The second section is a detailed description of the physical diagnosis of the respiratory system and it is in this part that Professor Martini's book is weakest; not because of lack of material but because of the manner of presentation.

The section devoted to the physical diagnosis of the circulatory system is well arranged and well worth the close attention of the reader. The same may be said of the section on the examination of the abdominal organs. The observations and the descriptions are quite clear.

A detailed outline of a medical history completes the book. This outline is well done and the form is similar to that generally used by the medical profession.

Dr. Martini has compiled a small, but within its limits, a complete treatise on the principles and practice of physical diagnosis. All of the pertinent facts are presented. The book can well take its place as one that may be used by elementary students of physical diagnosis.

M. J.

Chronic Intestinal Toxemia and Its Treatment. By JAMES W. WILTSIE. 268 pages. William Wood and Co., Baltimore. 1938.

The author of this monograph has made many contributions to the literature of colonic irrigations and is as well fitted as any physician to present the point of view of those who stress the importance of intestinal toxemia and who believe in the efficacy of colonic lavage as a form of treatment. There has been no doubt a good deal of prejudice for and against this point of view. Those who wish to examine the evidence *pro* may read Dr. Wiltsie's book with profit.

M. C. P.

The Human Body. By LOGAN CLENDENING, M.D. 443 pages; 16 × 24 cm. Alfred A. Knopf, New York. 1937. Price, $3.75.

Dr. Clendening, in the letter to Dr. P. T. Bohan, which forms the preface and dedication of this book, states that it was written "to make intelligible some of the intricacies of the human body for the adult and otherwise sophisticated reader." Actually, he has produced an outline of human biology, physiology, anatomy, and pathology, flavored throughout by his vigorous, sometimes acid, but always interesting personal philosophy.

The work is divided into four sections titled: The Human Body as a Unit; The Human Body as an Organism for the Conversion of Food and Air into Energy and into Tissue; The Human Body as an Organism for the Reproduction of Its Own Kind; and The Human Body and Disease. Each section, as may be surmised, takes up a different aspect of the relation of the body to itself and its environment.

Those who are familiar with Dr. Clendening's virile style and acquainted with the worth of his medical writing, need not be told that he is an ideal author for a popular work of this type. It fulfills all expectations, and is fully recommended.

T. N. C.

COLLEGE NEWS NOTES

Annual Meeting of the American College of Physicians

New Orleans, La., March 27–31, 1939

The 1939 meeting of the American College of Physicians will be held in New Orleans at a particularly delightful time of the year. The weather is usually warm, the sun shines brightly and all the spring flowers are out in all their glory. The New Orleans members of the College are looking forward with a great deal of pleasure to welcoming the Fellows throughout the country at this annual convocation.

The Executive Committee and the Sub-Committees consist of the following Fellows:

General Sessions and Lectures

William J. Kerr, President

General Chairman

J. H. Musser

Committee on Arrangements

P. H. Jones
Allan Eustis
Edgar Hull
Robert Bernhard
John Lanford
Randolph Lyons

Committee on Clinics and Demonstrations

P. H. Jones, Chairman

O. W. Bethea
J. M. Perrett
W. L. Smith
C. S. Holbrook
W. R. Wirth

Committee on Transportation

Edgar Hull, Chairman

L. A. Monte
G. R. Williamson
R. H. Bayley

Committee on Entertainment

Robert Bernhard, Chairman

Anees Mogabgab
D. N. Silverman
Ben Heninger
Grace Goldsmith

Committee on Auditorium

Allan C. Eustis, Chairman

C. Tripoli
G. M. Decherd

Committee on Publicity

John Lanford, Chairman

M. E. Bass
C. J. Bloom
Clyde Brooks
Maud Loeber

C. W. Duval

Committee on Round Tables

Randolph Lyons, Chairman

C. C. Bass
J. M. Bamber

J. C. Cole

Ladies Entertainment Committee

Mrs. C. Grenes Cole, Chairman

The Executive Committee and its subdivisions are arranging for the round table conferences, the clinics at the hospitals and the entertainment for the visiting members. To speak of the last first, it might be said that the Smoker will be held on Monday evening. It will be held at the Roosevelt Hotel, which will be the headquarters for the meeting. On Tuesday night there will probably not be any session, but the opportunity will be given to the Fellows of enjoying the pleasures and hospitality of the city. Wednesday night the Convocation will be held at the Hotel Jung, which is designated as Convocation hotel, and will be followed by the President's Reception. On Thursday night will be held the annual Banquet, at which it is hoped to have two of the literary lights of New Orleans address the diners.

The arrangements of the meetings will be different than they were last year in New York. On Tuesday and Thursday mornings from 9:00 to 11:00 dry clinics will be held in the Auditorium. On the same days from 10:00 to 12:00 will be held round table conferences. The dry clinics will be held in part by the local men and in part by invited guests. For the round tables so far the following speakers have promised to conduct these meetings: in cardiology, Dr. Fred M. Smith, F.A.C.P., Iowa City; nutrition, Dr. James McLester, F.A.C.P., Birmingham; blood dyscrasias, Dr. Roy R. Kracke, Emory University, Ga.; radiology, Dr. B. R. Kirklin, F.A.C.P., Rochester, Minn.; bacterial chemotherapy, Dr. P. H. Long, Baltimore; gastro-enterology, Dr. Lay Martin, F.A.C.P., Baltimore; nephritis, Dr. William S. McCann, F.A.C.P., Rochester, N. Y. In addition to these speakers, it is planned to have an outstanding surgeon conduct a round table conference on medico-surgical problems. The infectious diseases will also be considered; a pediatrician has been invited and a psychiatrist. There will also be held a round table conference on the animal parasitic diseases. There will be a sufficient number of leaders in these conferences to ensure relatively small groups, so that personal contacts between speaker and audience may be maintained. On Wednesday and Friday mornings there will be hospital clinics held at the Charity Hospital, Touro Infirmary, Baptist Hospital and possibly one of the other hospitals. The Charity Hospital's new building will not be completed, but the clinics will be held in the adjoining medical school building of Louisiana State University. Because of the limitation in hospital accommodations, on these same mornings from 10:00 to 12:00 lectures will be delivered at the Auditorium. It will be noted there is some overlapping of the hours. This has been done deliberately, in order to permit a greater selection of special features than otherwise would be possible.

The General Sessions will be from 2:00 to 5:00 in the afternoon and Monday night from 8:00 to 10:00. The headquarters hotel will be the Roosevelt Hotel; and, if the Fellows wish to stay in this hotel, reservations should be made promptly, as already the greater part of the hotel has been filled. The convocation hotel will be the Jung Hotel. This hotel is a splendid caravansary. The room in which the Convocation will be held has just been constructed and is a truly beautiful room. There are many other good hotels in New Orleans, practically all of them centrally located only a few blocks from the Auditorium and Charity Hospital, but it is urged that the Fellows make their reservations as early as possible, as there are a large number of tourists in New Orleans at this time of year and sometimes it is difficult to secure accommodations.

Mrs. C. Grenes Cole, wife of Dr. Cole, who is a former president of the Orleans Parish Medical Society, and at present president of the Woman's Auxiliary of the Society, has arranged for a series of delightful entertainments for the women visitors. These will include trips through the old French Quarter with guides, river rides, luncheons, teas, trips to some of the old plantation homes and other entertainments which will keep the wives and feminine members of the family of the members busy during the scientific sessions.

President Kerr reports that an excellent program of General Sessions and special lectures is being arranged, which will present important recent and new contributions from the clinical sciences, the practice of medicine, including titles from the fields of pediatrics, neuropsychiatry, dermatology and syphilology, and surgery. The speakers are being chosen with great care, not only for their subjects but also for their ability to present them well. Officers, Regents and Governors of the College, as well as medical schools and hospitals, have been canvassed by President Kerr, and he has received a fine response concerning available subjects and the desires of those who know the needs.

Postgraduate Courses

In further pursuance of the policy of organizing and offering special limited postgraduate courses especially for members of the College and those preparing either to meet the requirements for certification by the American Board of Internal Medicine or the requirements for Fellowship in the College, the American College of Physicians will conduct such a series of courses during the two weeks, March 13 to 25, inclusive, 1939, preceding the Annual Session of the College. At a meeting of the Committee on Postgraduate Courses, consisting of Dr. Hugh J. Morgan, F.A.C.P., Chairman, Nashville, Tenn., Dr. Charles Sidney Burwell, F.A.C.P., Boston, Mass., Dr. Joseph A. Capps, F.A.C.P., Chicago, Ill., Dr. Charles H. Cocke, F.A.C.P., Asheville, N. C., Dr. William J. Kerr, F.A.C.P., San Francisco, Calif., and Mr. E. R. Loveland, Executive Secretary of the College, at New York City on October 16 the following tentative outline of courses was determined upon:

A. Baltimore, Md. (under chairmanship of Dr. M. C. Pincoffs, F.A.C.P.), Johns Hopkins University School of Medicine and the University of Maryland School of Medicine coöperating.
1. General Medicine
2. Cardio-Respiratory Diseases

B. Chicago, Ill. (under chairmanship of Dr. James G. Carr, F.A.C.P.)
3. General Medicine, University of Illinois College of Medicine
4. Cardiology, Northwestern University Medical School
5. Research Review, University of Chicago Clinics

C. St. Louis, Mo. (under chairmanship of Dr. David P. Barr, F.A.C.P.) Washington University School of Medicine

6. Cardiology
7. Internal Secretions
8. Dermatology and Allergy in Relation to Internal Medicine

D. Nashville, Tenn. (under chairmanship of Dr. John B. Youmans, F.A.C.P.)
Vanderbilt University School of Medicine
9. General Medicine

The response to the program conducted last year in Boston, New York and Philadelphia, was so gratifying that this activity is being extended. Keen interest has been indicated in other special courses, but inasmuch as the program is still in its experimental stage, the Committee has determined not to overexpand the number of courses given. These courses will be made available at minimum cost, because the College itself will assume full responsibility for promotion, advertising, printing and registration, as its contribution to its members. It is anticipated that the registration fee for each course will be $40.00, and that the detailed bulletin of the courses will be ready for distribution by January 1.

The Royal Australasian College of Physicians

Dr. Noble Wiley Jones, F.A.C.P., Portland, Ore., Second Vice President, will be the official representative of the American College of Physicians at the Inauguration of the Royal Australasian College of Physicians, to be held in Sydney, Australia, December 15, 1938. This body has been formed among the physicians of Australia and New Zealand. Dr. Allan S. Walker, 185 Macquarie St., Sydney, Australia, is the Honorary Secretary.

Gifts to the College Library

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Reprints

Dr. L. Minor Blackford (Associate), Atlanta, Ga.—four reprints;
Dr. Ralph O. Clock, F.A.C.P., Scarsdale, N. Y.—one reprint;
Dr. Perk Lee Davis (Associate), Philadelphia, Pa.—three reprints;
Dr. Lorenz W. Frank, F.A.C.P., Denver, Colo.—four reprints;
Dr. Paul J. Hanzlik, F.A.C.P., San Francisco, Calif.—twenty-eight reprints;
Dr. M. Coleman Harris, F.A.C.P., New York, N. Y.—one journal;
Dr. Jerome George Kaufman (Associate), Newark, N. J.—two reprints;
Dr. Oliver M. Layton, F.A.C.P., Fond Du Lac, Wis.—one reprint;
Dr. James B. McLester (Associate), Birmingham, Ala.—four reprints;
Dr. F. M. Pottenger, F.A.C.P., Monrovia, Calif.—one reprint;
Dr. Willard C. Rappleye, F.A.C.P., New York, N. Y.—one reprint;
Dr. William B. Rawls, F.A.C.P., New York, N. Y.—one reprint.

From the College Archives

The most valuable addition to the Archives of the College obtained recently is a copy of the "Transactions of the American Congress on Internal Medicine, 1917," donated to the College Library by Dr. Clement R. Jones, F.A.C.P., Pittsburgh, Pa., former Treasurer of the College. The "Transactions" were published in book form, and give early details concerning the "Second Scientific Session" conducted under the auspices of the American Congress on Internal Medicine, which was the affiliated

society conducting the annual programs and acting as a feeder to College membership. The Pittsburgh proceedings disclose many of the early problems in the organization of the American College of Physicians, and in a published obituary it is disclosed that Dr. Heinrich Stern, the first Secretary General of the College, was the chief motivating spirit behind the formation of both the American Congress on Internal Medicine and the American College of Physicians. Quoting therefrom, "Dr. Stern conceived the idea of a congress of internists, that should not be limited to those in prominent teaching positions but that should be open to all of the profession who were particularly interested in internal medicine—and among those, who by meritorious work, study and investigation had done something for the good of humanity and the profession, a certificate, causa honoris, in the American College of Physicians, should be given. These dreams and ideals he repeated time and again to his friends until finally he interested some of his professional brethren who saw the truth and possibilities of his concept. After much labor and deliberation, stimulated and abetted by his enthusiasm, the American Congress on Internal Medicine and its exemplar—The American College of Physicians—were formed. When these were fully organized and had justified his prophecy, it was denied him, as it was to Moses of old, that he should see the promised land in the progress and brilliant success of these organizations which will be permanent memorials of their founder and the ideals of the internists and consultant which have become actualities."

Sectional West Virginia Meeting, American College of Physicians

A joint meeting of the West Virginia members of the American College of Physicians and the West Virginia Heart Association and the Cabell County Medical Society was held at Huntington, W. Va., October 13, 1938. Dr. Oscar B. Biern, F.A.C.P., Huntington, and Dr. P. A. Tuckwiller (Associate), Charleston, are President and Secretary, respectively, of the West Virginia group of the College. Dr. Tuckwiller is also Secretary of the West Virginia Heart Association and Dr. R. J. Condry, F.A.C.P., Elkins, is President. The program was as follows:

10:30–12:00 St. Mary's Hospital
Demonstration of Heart Cases
Technic of Lateral Fluoroscopy, Lateral Chest Plates, etc.)
Dr. Sam Brown, Cincinnati, Ohio; Dr. A. Carlton Ernstene, Cleveland, Ohio; Dr. Julien Benjamin, F.A.C.P., Cincinnati, Ohio.

2:00 p.m. Ball Room Hotel Governor Cabell
Roentgenological Diagnosis of Heart Disease
Dr. Sam Brown, Cincinnati, Ohio.

3:00 p.m. Ball Room Hotel Governor Cabell
Common Errors in Cardiac Diagnosis
Dr. A. Carlton Ernstene, Cleveland, Ohio.

4:00 p.m. Ball Room Hotel Governor Cabell
Electrocardiographic Slides Demonstration
Dr. Julien Benjamin, F.A.C.P., Cincinnati, Ohio.

6:30 p.m. Dinner—Hotel Governor Cabell

8:30 p.m. Ball Room Hotel Governor Cabell
Joint meeting of the West Virginia Heart Association, West Virginia Branch of the American College of Physicians and the Cabell County Medical Society.
Surgery of the Heart
(With motion pictures and lantern slide demonstration)
Dr. Calude S. Beck, Professor of Surgery, Western Reserve University, Cleveland, Ohio.

The College of Physicians of Philadelphia has instituted a program of semi-public lectures to the laity during the coming winter. Dr. Alfred Stengel, M.A.C.P., on November 18 will deliver one of these addresses on "Currents and Counter-Currents in the Progress of Medicine."

Dr. E. J. G. Beardsley, F.A.C.P., Philadelphia, was the guest speaker at the initial autumnal meeting of the Hudson County (N. J.) Medical Society at Jersey City, on October 4. A clinical conference was held at the Medical Centre, Jersey City.

Dr. Beardsley also addressed the Burlington County (N. J.) Medical Society on October 13 at the first meeting of the autumn, which was held at the Moorestown Country Club, Moorestown, N. J., on "Routine and Systematic Physical Examinations versus Intuitive Diagnoses."

Dr. J. Merriman Lynch (Associate), formerly of Panama City, is now engaged in practice in Pasadena, Calif., limiting his work to Internal Medicine and Tropical Diseases. He was recently appointed Instructor in the University of Southern California School of Medicine.

In tribute and appreciation to Dr. F. M. Pottenger, F.A.C.P., Monrovia, Calif., there has grown a custom of an annual home-coming of ex-patients at the Pottenger Sanatorium. More than two hundred patients, former patients and friends foregathered at the Sanatorium on September 25. Representatives were present from the various years since the establishment of the Sanatorium in 1903, including one ex-patient who was at the Sanatorium twenty-five years ago. It is the custom of the Sanatorium to keep in touch with all former patients. Contact is still maintained with eleven of the thirty-six patients who were treated at the Sanatorium in 1904, one year after its founding. Since establishment of the Sanatorium, more than 12,000 patients have been treated there. When the Sanatorium was opened in 1903, the death rate from tuberculosis was about 200 per 100,000 population. Today it is approximately 53 per 100,000 population. In Dr. Pottenger's address at the foregathering, he predicted that because of the progress in treatment and education, the death rate from tuberculosis may be further reduced in the next decade to 20 per 100,000 population.

Dr. August A. Werner, F.A.C.P., St. Louis, addressed the Mississippi Valley Medical Society at Hannibal, Mo., September 30, on the subject of the anterior-pituitary gonad relationship in the female.

Dr. Lowell D. Snorf, F.A.C.P., Assistant Professor of Medicine at Northwestern University Medical School, Chicago, addressed the ninety-fourth annual meeting of the Northwestern Ohio Medical Association October 4 on "Functional Disorders of the Intestinal Tract."

Dr. George W. McCoy, F.A.C.P., Surgeon, U. S. Public Health Service, is now on duty in New Orleans as head of the Department of Preventive Medicine and Public Health, Louisiana State University Medical Center.

Dr. A. C. Woofter (Associate), Parkersburg, W. Va., has been appointed physician in charge of the health department of the Parkersburg city-county schools.

Dr. Horace K. Richardson, F.A.C.P., Assistant Medical Director of The Austen Riggs Foundation, Stockbridge, Mass., gave the annual Mental Hygiene Lecture at Vassar College on October 10, 1938.

Dr. Walter F. Donaldson, F.A.C.P., Secretary, has announced that the eighty-ninth annual session of the Medical Society of the State of Pennsylvania will be held in Pittsburgh, October 2–5, 1939.

Dr. Frank L. Jennings, F.A.C.P., for a number of years Associate Medical Director of the Glen Lake Sanatorium, Oak Terrace, Minn., and Instructor in Medicine, University of Minnesota Medical School, Minneapolis, has been named Superintendent of the Marion County (Ind.) Tuberculosis Hospital at Sunnyside. He succeeds Dr. A. E. Hubbard, who died September 15. Dr. Jennings is a graduate of Syracuse University College of Medicine and is a past president of the Mississippi Valley Sanitarium Association. For three years he was assistant physician at the New York State Sanitarium at Raybrook, N. Y., having gone to the Glen Lake Sanatorium in 1917. This institution has been enlarged from a 50-bed capacity, when Dr. Jennings first was associated with it, to one of 700 beds.

The Liaison Committee and the Committee on Postgraduate Education of the American College of Physicians were invited to confer with like committees of the American College of Surgeons at the latter's annual session in New York City, beginning October 17. The delegates from the American College of Physicians were also invited to attend the 21st Annual Hospital Standardization Conference. The committees will make a survey and report to the Board of Regents on any matters of mutual interest and possible coöperation between the two Colleges.

The 49th annual convention of the Association of Life Insurance Medical Directors of America was held in Philadelphia October 20–21, under the presidency of Dr. Samuel B. Scholz, Jr., F.A.C.P., Medical Director of the Penn Mutual Life Insurance Company of Philadelphia. Every life insurance company with home offices in the United States or Canada was invited to participate in the discussions. Dr. Harry E. Ungerleider (Associate), Assistant Medical Director of the Equitable Life Assurance Society, New York, N. Y., presented a paper on "A Study of the Transverse Diameter of the Heart Silhouette With Prediction Table Based on the Teleoroentgenogram" and Dr. J. Hamilton Crawford, F.A.C.P., Professor of Clinical Medicine at Long Island College of Medicine, and Dr. C. E. de la Chapelle, F.A.C.P., Assistant Professor of Medicine, New York University College of Medicine, led the discussion.

The Sixteenth Annual Scientific Session of the Academy of Physical Medicine was held in Washington, D. C., October 24–26, 1938. Among members of the College contributing were the following:

Dr. William A. Swalm, F.A.C.P., Philadelphia, "Gastroscopic Control in the Treatment of Diseases of the Stomach";

Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., "Biological Aspects of Light Therapy."

The Sixth Annual Assembly of the Omaha Mid-West Clinical Society was held October 24–28, under the Presidency of Dr. Bryan M. Riley, F.A.C.P. The following members of the College participated in the program:

Dr. Henry L. Bockus, F.A.C.P., Philadelphia, leader of a round table on "The So-Called Irritable Colon," a formal paper on "Practical Application of Recent Advances in Our Knowledge of Liver Function," a formal paper on "Diagnosis and Treatment of Chronic Gastritis" and a clinic on "Gastrointestinal and Hepatic Disorders";

Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia, Pa., leader of a round table on "The Importance of Hypotension," formal papers on "Principles of Diagnosis and Treatment of Diseases in the Elderly" and "Recognition and Treatment of Anemia Due to Increased Blood Destruction" and a clinic on "Hematology";

Dr. John F. Gardiner, F.A.C.P., Omaha, radio broadcast, "Overweight";

Dr. G. A. Young (Associate), Omaha, scientific exhibit on "Convulsions—Their Treatment and Therapeutic Use in Psychoses";

Dr. A. F. Tyler, F.A.C.P., Omaha, scientific exhibit (motion picture in color), "Radiation Therapy";

Dr. F. Lowell Dunn, F.A.C.P., Omaha, scientific exhibit, "Arthritis";

Dr. E. L. MacQuiddy (Associate), Omaha, scientific exhibit, "Lung Changes Produced by Chronic Nitric Oxide Inhalation and by Dust Inhalation";

Dr. Chester Thompson (Associate), Omaha, a lecture on "Errors in Cardiac Diagnosis";

Dr. M. W. Barry, F.A.C.P., Omaha, a lecture on "Treatment of Cardiovascular Syphilis";

Dr. H. A. Wigton, F.A.C.P., Omaha, a lecture on "Encephalitis—Types and Treatment";

Dr. Ernest Kelley, F.A.C.P., Omaha, a lecture on "The Use of Metrazol in Mental Diseases";

Dr. John F. Gardiner, F.A.C.P., Omaha, a lecture on "The Knowledge Required of the General Practitioner in the Present Day Treatment of Pulmonary Tuberculosis";

Dr. John R. Kleyla, F.A.C.P., Omaha, a lecture on "Broncho-Sinusitis."

Dr. Lauren H. Smith, F.A.C.P., Associate in Psychiatry, University of Pennsylvania School of Medicine, and Executive Medical Officer, Institute of the Pennsylvania Hospital, has recently succeeded Dr. Earl D. Bond as Physician-in-Chief and Administrator of the Pennsylvania Hospital's Department of Mental and Nervous Diseases and as Director of the Institute.

Dr. N. S. Davis, III, F.A.C.P., Chicago, is President of the Chicago Academy of Sciences, having formerly acted as Secretary. During June, 1938, Dr. Davis was also made President-Elect of the Chicago Medical Society. On November 3, 1938, Dr. Davis discussed "Treatment of Arteriosclerotic Heart Disease" before the Southern Illinois Medical Association at East St. Louis, Ill., and on November 15 he presided at a clinical conference at a special meeting of the Fellows and Associates of the College of southern Illinois. This sectional meeting of the College was held at Decatur, under the chairmanship of Dr. Samuel Munson, F.A.C.P., Governor of the College for southern Illinois.

OBITUARY

DR. LESTER I. LEVYN

Lester I. Levyn (Fellow, A.C.P., 1922) died at his home in Buffalo, N. Y., on June 24, 1938, after an illness of three years. He was a lifelong resident of Buffalo, having been born there on December 28, 1887. He was graduated from the University of Maryland Medical School in 1909.

Following his graduation he went into the general practice of medicine for a few years. He then went abroad for the study of roentgenology, especially in the Berlin and London clinics. He followed this with some postgraduate work at the Harvard University Medical School. On his return he limited himself to the practice of roentgenology, which he continued to the time of his death.

He was a member of the following societies: The Buffalo Radiological Society; The Buffalo Academy of Medicine; The Erie County and New York State Medical Societies; The American Medical Association; The American Roentgen Ray Society and the Radiological Society of North America. He became a Fellow of the American College of Physicians in 1922.

Dr. Levyn carried on an extensive private practice and in addition was, for many years, director of the Department of Roentgenology of the Deaconess Hospital. His illness, leukemia, forced him to relinquish this post about two years ago. During his career he made many contributions to the roentgenological literature. He was particularly interested in cholecystography and published many articles pertaining to it.

Early in 1935 he learned of the fatal nature of his last illness. In spite of this knowledge he carried on his practice and hospital work with the same skill and efficiency as ever. To his intimates and associates, who knew of his affliction, his fortitude and courage were the subject of great admiration. Within the last year he continued his publications, preparing and delivering a paper at the International Congress of Radiology.

In addition to his professional interests, Dr. Levyn was active in many local enterprises. He was particularly interested in sectarian charitable institutions and served on many boards up to the time of his death.

He was unmarried and is survived by a sister and brother. In his death, both the profession and the community have lost a valuable and stimulating member.

NORMAN HEILBRUN, M.D.